Research

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Quantum aspects of evolution: a contribution towards evolutionary explorations of genotype networks via quantum walks

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Quantum biology seeks to explain biological phenomena via quantum mechanisms, such as enzyme reaction rates via tunnelling and photosynthesis energy efficiency via coherent superposition of states. However, less effort has been devoted to study the role of quantum mechanisms in biological evolution. In this paper, we used transcription factor networks with two and four different phenotypes, and used classical random walks (CRW) and quantum walks (QW) to compare network search behaviour and efficiency at finding novel phenotypes between CRW and QW. In the network with two phenotypes, at temporal scales comparable to decoherence time T_D , QW are as efficient as CRW at finding new phenotypes. In the case of the network with four phenotypes, the QW had a higher probability of mutating to a novel phenotype than the CRW, regardless of the number of mutational steps (i.e. 1, 2 or 3) away from the new phenotype. Before quantum decoherence, the QW probabilities become higher turning the QW effectively more efficient than CRW at finding novel phenotypes under different starting conditions. Thus, our results warrant further exploration of the QW under more realistic network scenarios (i.e. larger genotype networks) in both closed and open systems (e.g. by considering Lindblad terms).

1. Background

Quantum biology is a novel discipline that uses quantum mechanics to better describe and understand biological phenomena [1–3]. Over the last 15 years, there have been theoretical developments and experimental verifications of quantum biological phenomena [2,4] such as quantum tunnelling effects for the efficient workings of enzymes at accelerating biological metabolic processes [5], and quantum superposition for efficient energy transfer in photosynthesis [6]. The area of quantum evolution [7], in which it is suggested that DNA base pairs remain in a superposition by sharing the proton of hydrogen bonds, still remains speculative and has practically stagnated since its theoretical inception 20 years ago [7,8]. However, recent theoretical developments on quantum genes (e.g. [9]) suggest that further exploration of the superposition mechanism in evolution is worth undertaking.

1.1. Theoretical framework: quantum measurement device

From biological principles, genes do not vary in a continuous fashion, they are digital objects (i.e. a sequence of discrete nucleotides); such discontinuity renders mutations as quantum jumps between different states or possible

Figure 1. (a) A correct A–T base pairing; (b) an A–T base pair with their hydrogen protons switched. (c) A correct G–C base pair and (d) two tautomeric base pairs (modified from [4]).

variations of a gene [10,11]. In other words, genes function as discrete packets, which are akin to quantum digital objects over which computations are performed [12]. Hence, the theoretical framework of quantum mechanics offers two characteristics that are fundamental for life and its evolution: digitalization and probabilistic variation among the discrete states a quantum system can take (e.g. DNA nucleotides [12]).

Focusing on DNA, the genetic code is ultimately determined by hydrogen bonds of protons shared between purine and pyrimidine nucleotide bases [7]. Nucleotides have alternative forms known as tautomers, where the positions of the hydrogen protons in the nucleotide are swapped, changing nucleotide chemical properties and affinities [13,14]. Such changes make the DNA polymerase enzyme to sometimes pair wrong nucleotides (e.g. a tautomeric thymine with a guanine), generating mutations that change the genetic information and possibly the encoded protein (figure 1) [4,7]. An important consequence of this process, since genes can be thought of as quantum systems, is that nucleotides' hydrogen bridges can be described as a quantum superposition, where protons can be found at both sides of the DNA chain at the same time (i.e. the physical variable in a superposition is the hydrogen proton joining DNA nucleotides; quantum genes), hence allowing the system to be described by a wave function [7,11]. A measurement (e.g. a chemical, UV light from the environment) can collapse the wave function producing either a normal base pair or a mutation [4,7]. Thus, quantum processes can be of relevance at understanding mutation dynamics when influenced by the surrounding environment (i.e. selective factors; figure 2) [9,11], playing an important role in the exploration of evolutionary space (e.g. n -dimensional genotype networks, as introduced shortly in this paper).

1.2. Theoretical framework: n -dimensional genotype networks

A theory based on n -dimensional genotype space at different levels of biological organization (e.g. metabolism, gene

regulation) has been developed to understand the evolution of innovations [15,16]. A genotype network implies the existence of a vast connected network of genotypes (nodes in a network) that produces the same phenotype [17]. Genotypes in a genotype network can share little similarity (e.g. lower than 25%) and still produce the same phenotype [15]. To understand the concept of a genotype network, we will focus on metabolic reactions (figure 3) [15].

A metabolic genotype is the total amount of chemical reactions that can be performed by the enzymes synthesized by an organism's genotype [15]. If we use digital (i.e. binary) categorization, then we can classify a metabolic genotype as a string of binary flags, indicating if the genotype has the information to synthesize a product that performs a metabolic reaction (represented by 1) or not (represented by 0; figure 3). From current information, we know there are about 10^4 metabolic reactions (no organism can perform all of them [18]), in which case, we would have in binary space with $2^{10,000}$ different possible metabolic genotypes, which is a large universe of possibilities available for evolution to explore [16,18,19]. Hence, the genetic space of metabolic genotypes is composed of all possible binary strings of length 10^4 , in this case, a total of $2^{10,000}$. A way to measure differences between two metabolic genotypes in this vast space is to use the fraction of reactions that are not catalysed by one genotype in reference to the other; the letter D represents such a measure [20]. The maximal value $D = 1$ would be achieved when the two metabolic genotypes do not have any reaction in common and $D = 0$ when they have identical metabolic genotypes (i.e. they would encode the same products or enzymes). Two metabolic genotypes would be neighbours if they differ only by a single reaction (a 1 in our binary coding of metabolic genotypes). Hence, the neighbourhood of a metabolic genotype is composed of all those genotypes that differ by exactly one reaction from it; there would be as many neighbours as there are metabolic reactions (figure 4). Considering the different possible metabolisms one step away from a focal one, each neighbourhood would be a large collection of metabolic genotypes organized in a

Figure 2. Decoherence process of a quantum wave function with three possible states under the influence of an environmental factor (measurement). (a) Three possible bacterial cell states (we only use three for simplicity, but it can include all n -dimensional neighbours in a genotype network, figure 4), represented by state vectors. (b) Superposition of the three state vectors, which results in a linear combination of eigenfunctions each with a probability C_i . (c) The quantum wave function collapses towards the fit cell variant (i). When measuring time to decoherence (ii), all states of the quantum superposition under no selective conditions (i.e. no lactose) are indistinguishable by the bacterial cell, eventually collapsing to any of the possible states at T_{D1} . However, when the environmental factor is present (i.e. lactose present), the time to decoherence will be shorter (T_{D2}) and biased towards fit variants (i.e. adaptive mutation) able to grow and reproduce. Those bacterial cells that do not reduce towards the adaptive state will remain in a quantum superposition. Thus, the quantum superposition will collapse to the adaptive state with higher probability under the environmental adaptive conditions (i.e. lactose present) compared to the time it takes to appear under non-selective environments ($T_{D2} < T_{D1}$).

Figure 3. (a) A list of metabolic reactions; a 1 next to a reaction indicates that an organism has such a metabolic path otherwise there is a 0. (b) A list of resources that can be used (1) or not (0) by a metabolic genotype in order to synthesize all required biomolecules (see the text for details; modified from [15]).

hyper-dimensional cube. With this, we build an n -dimensional network, where each genotype is a node in the network and the edges represent mutational steps, nodes connected by an edge differ exactly by one mutation (figure 4) [16,20].

A metabolic phenotype is represented by all the environmental energy sources (e.g. glucose, methane) that can be

used by a metabolic genotype to synthesize all biomolecules (e.g. amino acids, nucleotides) required for survival (figure 3). The metabolic phenotype can also be categorized as a binary string, a 1 represents a genotype network that can synthesize all required biomolecules relying solely on that specific source and a 0 otherwise; a phenotype with multiple ones means a metabolism that can produce all needed elements from many different sources [15]. To calculate the number of possible phenotypes, we do the same as for metabolic genotypes; we raise two to the power of all the known different energy sources available. The set of those metabolic genotypes that have the same phenotype is what constitutes a genotype network. It has been shown computationally that similar (i.e. neighbours), as well as very dissimilar genotypes (as different as 80% of their metabolic reactions), can still preserve the same phenotype, demonstrating that genotype networks are plastic and robust [21,22]. This is a good feature for evolving populations because browsing the vast genotypic space becomes feasible and moderately free of risk [18,20]. However, how can new features evolve when a vast exploration leads us to the same viable result or phenotype? When comparing the neighbourhoods of thousands of pairs of metabolic genotypes that are able to use the same energy source (i.e. they belong to the same phenotype network), but that are otherwise very different, it turns out that their

Figure 4. Representation of metabolic genotypes and phenotypes in different dimensions (modified from [15]). Networks in one (1D), two (2D) and three dimensions (3D), where vertices are labelled with the binary strings that correspond to each dimension (1, presence of metabolic pathway; 0, absence of metabolic pathway; figure 3). Two versions of a three-dimensional representation of a four-dimensional cube are shown (i.e. the shadow of a tesseract), each with its own section of a genotype network (i.e. network of white circles in the upper panel and network of black circles in the lower panel representing different phenotypes). Each line (i.e. link or edge) connecting two symbols represents a single mutational step. Genotype networks (those with same symbols) are vast across hyper-dimensions (genotype space), maintaining the same phenotype (i.e. robust to mutational changes across the network) even if genotype similarity is low (e.g. nodes on opposite sides of the genotype network). On the right side, we unfold the four-dimensional cubes into two-dimensional images for clarity. There, neighbourhoods at different places of the genotype space are very diverse (different symbols inside dashed circles), which opens opportunities to find novel phenotypes. Some of the same evolutionary novelties can also be found at different neighbourhoods, allowing for convergence. Each genotype network is connected to an n -number of other genotype networks via extra-dimensional bypasses (black double lines connecting genotype networks belonging to different phenotypic networks).

neighbourhoods are very different and diverse (i.e. novel phenotypes in one neighbourhood might not be present in other neighbourhoods of the same genotype network (figure 4) [16]. As the number of changed metabolic reactions increases, so does the number of unique phenotypes in a neighbourhood, opening a bounty of novel phenotypes to an evolving population [20]. Furthermore, when comparing two genotype networks (i.e. networks that produce different phenotypes), the distance in genotype space that needs to be traversed to find a novel phenotype is rather small (i.e. the number of edges or mutational steps in the network separating nodes or genotypes with different phenotypes), raising the odds of finding novel traits (figure 4) [16,22]. More impressive yet is the fact that networks other than metabolism, such as transcriptional regulatory circuits [23,24] and the development of novel molecules [25–28], have the same basic structure [15].

There is no true randomness as originally conceived in Darwinian evolutionary theory (e.g. [29–32]). A series of experiments have shown that mutations are not completely random (figure 2) [29,31,33–38]; but see [39–41] for alternative explanations and examples on the process of adaptive mutations. Thus, we are ultimately interested in the potential effect that specific environmental conditions (i.e. probing agents that collapse the quantum superposition) have on the proposed genetic quantum system and the evolutionary pathway followed under such conditions (e.g. figure 5). Yet, we must first understand how quantum processes behave under non-selective (i.e. neutral and in closed systems) scenarios, so we can determine their relevance for evolution. Thus, in this paper, we explore how fast a quantum walk (QW) could explore an n -dimensional genotype network (*sensu* [15]) (i.e. a state space) and compare its performance with that of a classical random walk (CRW) (e.g. [42]).

Figure 5. A bacterial genotype network under two environments without lactose (top) and with lactose (bottom). The superpositions of three possible cell states and times to decoherence are depicted in the middle, to the right of each genotype network (see figure 2 for details). On the right-hand side, there are three alternative neighbourhoods of the original genotype network shown on the left. Different decoherence times (T_D) to reach the genotype capable of using lactose are illustrated, based on different paths followed on different neighbourhoods of the genotype network. The time to decoherence from the middle network on the right-hand side is shorter compared to the other two (i.e. $T_{D3} < T_{D2} < T_{D1}$).

Then, we explore under what scenarios of the state space (i.e. mutational steps between different phenotypes) may the quantum process be more efficient than the classical one at finding novel states (i.e. phenotypes) in n -dimensional genotype networks [16,43]. That is, we provide proof of concept that genotype networks are a suitable evolutionary fabric on which the earlier proposed quantum wave function [7,8] can operate, and then how the quantum wave function actually operates on such evolutionary fabric.

2. Material and methods

QW are more efficient at exploring one dimension (e.g. linear) and two dimension (e.g. grid networks) regular networks (i.e. squared) compared to CRW. CRW remains around the neighbourhood where it started expanding diffusively, whereas the superposition of QW produces a probability cloud expanding ballistically throughout the whole network [44,45].

The superposition property of QW would theoretically allow a more efficient exploration process throughout the network, given the previously proposed conditions by McFadden & Al-Khalili [7]:

- (1) The cell is a quantum measurement device that constantly monitors the state of its own DNA molecule. The environment will induce the collapse of the quantum wave function, rendering the current state of the DNA (i.e. the DNA sequence we actually observe when we obtain the base pairs of a genome or a gene), indirectly via the influence of the environment on the cell (e.g. chemical conditions of the cell's membrane and cytoplasm).
- (2) Following quantum mechanical jargon, the DNA molecule persists in a superposition of the hydrogen proton binding nucleotides (i.e. the different mutational options representing the wave function; see [11]). For instance, a wave function evolving to incorporate the correct and incorrect bases in a DNA position, as a superposition of states (i.e. mutated and unmutated states (e.g. the cytosine and thymine nucleotides in a DNA base pair)) in a daughter DNA strand; that is, the new DNA state achieved after replication of the genetic material ($|\Psi_G\rangle$) [7]:

$$|\Psi_G\rangle = \alpha|\Phi_{\text{not tunnelled}}\rangle|\text{Cytosine}\rangle + \beta|\Phi_{\text{tunnelled}}\rangle|\text{Thymine}\rangle.$$

- (3) The operational difference between the DNA and the cell is given by nucleotides (previous equation above) and amino acids, respectively [7]:

$$|\Psi_{\text{cell}}\rangle = \alpha|\Phi_{\text{not tunnelled}}\rangle|\text{Cytosine}\rangle|\text{Arginine}\rangle + \beta|\Phi_{\text{tunnelled}}\rangle|\text{Thymine}\rangle|\text{Histidine}\rangle.$$

- (4) An evolving or new DNA wave function (i.e. the current DNA superposition after the collapse of the wave function due to environmental influences) must remain coherent or stable for long enough time to interact with the cell's immediate environment, so the cell can act as a quantum device (figure 2).

2.1. Genotype network construction

We used a subset of the DNA transcription factor (TF) genotype networks from the sample file of Genonets server (<http://ieu-genonets.uzh.ch>) [46], which represent empirical data for the binding affinities of the Ascl2, Foxa2, Bbx and Mafk TFs in mice (figure 6) [47,48]. To filter genotypes with low binding affinities, we used the default value of the parameter τ ($\tau=0.35$), and we only allowed for single point mutations (i.e. mutations where a letter in the sequence is changed, no indels were allowed; see <http://ieu-genonets.uzh.ch/learn> for definitions and tutorials) [46]. Briefly, each node in the network represents a genotype with a specific TF phenotype (i.e. Ascl2, Foxa2, Bbx, Mafk), and the edges joining nodes represent mutational steps (i.e. two nodes joined by an edge are genotypes differing exactly by one position; in other words, only one mutation separates such nodes; see figures 3 and 4). We extracted the information of the genotype networks generated by Genonets, and performed all subsequent simulation analyses (described below) using the Mathematica software (Wolfram Research, Inc. 2020, Mathematica v. 12.1).

2.2. Genotype network exploration: closed systems (unitary evolution)

The n -dimensional genotype networks developed by Wagner and his collaborators use as an exploration mechanism CRW [15]. Here, we used QW in order to explore the importance of quantum superposition [42,49] as an evolutionary exploration device. Exploration of constructed networks was performed

Figure 6. A subset of TF genotype networks representing four-phenotype networks (different colours) extracted from Genonets server [46] and used for simulation analyses via QW and CRW.

using both a continuous CRW (e.g. [20]) and a continuous QW [50]. We used the QSWalk package developed under Mathematica to perform simulations on genotype networks [50]. The QSWalk package implements both CRW and continuous QW in arbitrary networks based on the so-called quantum stochastic walk that generalizes QW and CRW [50].

For simplicity, we considered undirected and unweighted networks, which were described by an adjacency matrix $\mathbf{A}_{ij}$ whose matrix elements are 1 if the nodes i, j are connected and 0 otherwise. For an undirected network, the adjacency matrix is symmetric $\mathbf{A}_{ij} = \mathbf{A}_{ji}$, which implies that transitions from any pair of neighbouring nodes are equally probable independently of the direction. For each node i , we define the out-degree $\text{out-Deg}(i) = \sum_j \mathbf{A}_{ij}$, which counts the number of nodes connected to it. The CRW is described by the vector $\mathbf{p}(t)$ whose components $p_j(t)$ give the probability of occupancy of node j . The temporal evolution of the probability vector is determined by the equation

$$\frac{d\mathbf{p}}{dt} = \mathbf{H}\mathbf{p},$$

where $\mathbf{H}$ is the matrix with entries defined as

$$\mathbf{H}_{ij} = \begin{cases} \gamma \mathbf{A}_{ij}, & i \neq j \\ -\gamma \text{out-Deg}(i), & i = j, \end{cases}$$

where γ determines the transition rate between neighbour nodes. We considered CRW beginning in node i , implying that the components of the initial vector are $p_k(t=0) = \delta_{ki}$.

For the QW, we considered a Hilbert space basis whose elements are associated with each node of the network $|i\rangle$. A general pure state can be written as $|\psi(t)\rangle = \sum_i c_i |i\rangle$, where $|c_i|^2$ is the probability of occupancy of node i . The dynamics of an initial configuration (similar to the CRW, we considered initial states with components given by $c_k = \delta_{ki}$) is given by the Schrödinger equation

$$\frac{d|\psi(t)\rangle}{dt} = \mathbf{H}|\psi(t)\rangle,$$

where $\mathbf{H}$ is a linear operator whose matrix elements are given by the same matrix introduced above

$$\langle i|\mathbf{H}|j\rangle = \mathbf{H}_{ij}.$$

We used DNA TF genotype networks with two (410 nodes) and four (927 nodes) different phenotypes, a representation of which is shown in figure 6. Following, we determined the mutation rate, γ_c and γ_Q , for the CRW and the QW, respectively.

2.3. Mutation rate, γ

The mutation rate between any pair of neighbouring nodes is mapped in the QSWalk package by a parameter, γ . For a CRW, the probability of mutation of a given node to a new node for very short times is $P_m = N_n \times \gamma_c \times t$, where N_n is the number of neighbouring nodes; in other words, the probability of remaining in the initial node decays exponentially. The average number of neighbour nodes in the networks used in our simulations is $N_n \sim 6.4 \pm 3.3$; therefore, the mutation rate per node is $m_r = 6.4 \pm 3.3 \gamma_c$. Experimental estimation of this mutation rate (i.e. the rate of mutation of a single gene) [51] yields $m_r = (4-9) \times 10^{-5}$ mutations/bp/cell generation. Assuming that a bacterial cell generation lasts around 1000 s (i.e. approx. 20 min), the mutation rate is $m_r = (4-9) \times 10^{-8}$ mutations $\text{bp}^{-1} \text{s}^{-1}$, which when equated to $6.4 \pm 3.3 \gamma_c$ allows obtaining an estimation of the order of parameter γ_c for the CRW of $\gamma_c = 10^{-9}-10^{-7} \text{s}^{-1}$.

By contrast, for a quantum system described by a Hamiltonian, it can be shown that for very short times, the probability of transition of a given node to a new node grows quadratically with time [52], $P_m = N_n \times (\gamma_Q \times t)^2$. In order for the QW to be consistent with the experimental mutation rate mentioned above, we estimate γ_Q , the mutation probability of a given node to a new node, by equating the quantum probability of node mutation with the classical probability at the decoherence time T_D (i.e. we considered $\gamma_c \times T_D = (\gamma_Q \times T_D)^2$, which gives $\gamma_Q^2 = \gamma_c / T_D$). Thus, to determine γ_Q , an estimation of T_D is necessary. According to [7], a rough estimation of the decoherence time is $T_D = 10^0-10^2 \text{s}$, which allows an estimation of quantum parameter $\gamma_Q = 10^{-6}-10^{-3}$. We selected representative values for γ_c and γ_Q to perform our simulations, $\gamma_c = 10^{-7} \text{s}^{-1}$ and $\gamma_Q = 10^{-4} \text{s}^{-1}$.

We follow [7] at using the Zurek model to estimate the decoherence time of genotypes (nodes in the network) superposition (T_D)

$$T_D \cong t_R \left(\frac{\lambda_T}{\Delta_x} \right)^2, \quad \lambda_T = \frac{\hbar}{\sqrt{2mk_B T}},$$

where m is the mass of a proton in a superposition of two Gaussian wave packets separated by a distance Δ_x , λ_T is the thermal de Broglie wavelength dependent and t_R is the time in which the wave packets dissipate the energy difference between coherent states [7,53].

For the small network consisting of 410 nodes and 2 phenotypes, we performed independent simulation runs with initial conditions that start from every single node of the Bbx

phenotype to the Foxa2 phenotype and compared the probability to find the Foxa2 phenotype as a function of time for CRW and QW, distinguishing the number of mutational steps (1, 2 or 3) needed to reach the new phenotype.

For the larger network (927 nodes and 4 phenotypes), we conducted simulations starting at nodes that were shared between different pair-wise combinations of the four different phenotypic networks. The aim was to compare the efficiency at which CRW and QW find novel phenotypes as a function of time (for the quantum process within the decoherence time T_D as calculated above) and of the initial position of a node within a genotype network in terms of the number of mutational steps (i.e. 1, 2 or 3 edges) needed to reach the new phenotype.

3. Results

3.1. Two-phenotype networks (Bbx and Foxa2; 410 nodes)

For this two-phenotype network, the linear dependence on time of the mutation probability of the CRW at short times induces a linear dependence on time of the probability of mutation to phenotype Foxa2 from nodes located one mutational step away (figure 7). For nodes located two or three steps away, the growth of the mutation probability to the new phenotype is slower. The same hierarchy in the probabilities is observed in the QW, the closer the node is located to the new phenotype, the larger the mutation probability to this phenotype is. Since the probability of an initial node to mutate to its neighbouring nodes grows quadratically in the QW model, the probability of mutation to a new phenotype is smaller in the QW model for very short times. But at the temporal scale of quantum decoherence, the CRW and QW probabilities become comparable. Furthermore, for larger times, QW probabilities become much larger than the classical ones, irrespective of the distance of the initial node to the new phenotype. These results show that at a temporal scale comparable or slightly larger than the decoherence time, the QW becomes more efficient than the CRW at finding the new phenotype.

3.2. Four-phenotype networks (Ascl2, Foxa2, Mafk and Bbx; 927 nodes)

Similar to the two-phenotype network simulation, for the CRW, there is a linear dependency on the probability of mutating to a novel phenotype as a function of time (figure 8). For the QW, at the temporal scale of quantum decoherence, the quadratic dependence of the probability of mutating makes the quantum process to have a higher probability of mutating to a novel phenotype under most conditions compared to the CRW. Such behaviour was observed regardless of the number of mutational steps (i.e. 1, 2 or 3) away from the novel phenotype (figure 8); the QW becomes more efficient than the CRW at finding the new phenotype. Furthermore, the QW became more efficient at finding novel phenotypes when the network increased in complexity (compare QW results from figures 7 and 8).

Figure 7. Simulation results for two-phenotype networks (Foxa2 and Bbx; figure 6). Probability of mutating to a novel phenotype as a function of time under the CRW (blue lines) and the QW (red lines) in log–log scale. Upper lines represent the average probability of simulations started at nodes that were one mutational step away from the novel phenotype; middle and lower lines are probability averages of nodes two and three mutational steps away from the novel phenotype, respectively. Shaded areas limited by dotted lines around the average lines represent the respective standard deviations of each simulation. The orange shaded area indicates the temporal estimates to decoherence time, and the vertical grey line is the time of a bacterial cell generation (i.e. approx. 20 min).

4. Discussion

The field of quantum biology has steadily grown over the last 15 years, in particular due to research focused on photosynthesis and enzymatic processes [2]. However, advances on how quantum mechanisms are relevant to biological evolution have stagnated during the last 2 decades, most likely due to a lack of an evolutionary framework where such quantum processes can be studied (but see [54–56]). Here, we have suggested that n -dimensional genotype networks (*sensu* [15]) represent an ideal ground where the relevance of quantum superposition for evolution can be explored. We have shown that under neutral scenarios (i.e. non-selective environments or closed systems), QW become more efficient at the temporal scale of decoherence time and under more complex scenarios (four-phenotype versus two-phenotype networks) than CRW. The QW model has exhibited a more diverse behaviour in terms of mutation probabilities to a novel phenotype, which is readily observed under a varied array of conditions (i.e. when starting the simulations at 1, 2 or 3 mutational steps away from novel phenotypes). Interestingly, the efficiency of QW at finding novel phenotypes increased when the network structure increased in terms of number of phenotypes and size. This suggests that as network complexity (i.e. number of phenotypes) and size (number of genotypes or nodes) increases, we can expect the QW mechanism to be a more efficient exploration device for evolution, given its superposition property. Thus, in order to move forward, the next step is to simulate QWs in open systems coupled to the environment, for example, using dissipative Lindblad terms (e.g. [11]).

If QW prove indeed to be more efficient than CRW in an open network system, then we would have a strong empirical framework to better understand mutation dynamics. Of course, our proposal (i.e. quantum evolution on n -dimensional networks) does not preclude the existence and commonality of Darwinian random and non-random mutations; it only provides a complementary framework to

Figure 8. Simulation results for four-phenotype networks (figure 6). Probability of mutating to a novel phenotype as a function of time under the CRW (left column) and the QW (right column) in log–log scale. Top panels show results for nodes one mutational step away from a novel phenotype, middle panels for nodes two mutational steps away from novel phenotypes and bottom panels started from three mutational steps away from novel phenotypes. The colour of the different lines indicates the phenotype network where the simulation started (figure 6). Shaded areas limited by dotted lines around the average lines represent the respective standard deviations of each simulation. Orange shaded areas indicate the temporal estimates to decoherence time, and the vertical dotted lines are the time of a bacterial cell generation (i.e. approx. 20 min).

a process that is not black and white (neo-Darwinian versus neo-Lamarckian processes), and we view it as an addition to an already well-established evolutionary construct that is actually a shade of grey [57]. An example of a theory expanding current evolutionary understanding of mutations is that of the writing phenotype [38], which suggests that mutations are non-random in the sense that there are genomic data showing specific regions with higher rates of mutations due to specific genome structures. Mechanisms generating such non-random mutations include non-allelic homologous recombination, non-homologous DNA end-joining, replication-based mechanisms and transposition (see [38]). In the cases of both n -dimensional genotype networks [58] and writing phenotypes [38], there are evolutionary constraints. In other words, non-random mutations (*sensu* [38]) are embedded in a genomic context that is modified as populations change from generation to generation. Hence, context-dependent evolutionary constraints are dynamic

because evolution shuffles the genomic context through time. Thus, the quantum proposed mechanism of exploration on n -dimensional networks needs further study to determine its relevance for evolutionary explorations within those constraints, e.g. by using dynamic adaptive networks [38].

According to Donald [59], the main flaw of the McFadden & Al-Khalili [7] model is ‘...the assumption of unitary wave function dynamics can provide an accurate description of the behavior of systems such as entire cells over significant time periods...’. This makes sense when one is trying to apply what happens in a single DNA base pair to an entire genome (thousands/millions of base pairs) with no negligible interaction with its surroundings (a fact that, as mentioned, shall force us to include quantum decoherence effects in an improved version of the evolutionary mechanism discussed here). However, there are three issues that make worth exploring a model of quantum coherence for evolution as the one proposed in this paper. First, the

construction on which we suggest the process of evolution to take place via quantum superposition is different from what was originally proposed by McFadden & Al-Khalili [7] and Ogryzko [8]. They suggested an entire cell, but here we are suggesting an evolutionary network, where two nodes (genotypes) are connected by a single mutation (link; see figures 3 and 4). In this sense, our n -dimensional genotype network provides a Hamiltonian for the unitary evolution requirement mentioned by Donald [59]. We consider this to be the advantage of using our framework to explore evolution via QWs, something that was missing from previous studies. Second, since Donald's [59] constructive criticisms, there have been advances that allow the understanding of full-genome evolution via quantum theory [56]. In other words, the criticism regarding that mutation may involve more than one DNA base pair can be overcome using more complex models akin to those proposed by Martin-Delgado [54] and Luo [56]. Finally, there is experimental evidence of quantum coherence in living organisms; biological systems have found a way to use quantum mechanical processes to solve many biological puzzles despite their watery, thermal and energy exchange: photosynthesis, enzyme dynamics, even the migratory mechanism by which birds orient themselves during their trips (as reviewed in [2,3]).

4.1. Philosophical extensions of quantum walk

4.1.1. Phylogenetics

This research field in biology uses a broad array of tools to reconstruct the history of life on Earth, which follows different optimality criteria (e.g. parsimony, maximum likelihood, Bayesian) and uses different types of information (e.g. molecules such as DNA, RNA and proteins, and morphological characters) to reconstruct such evolutionary history (for an introduction, see [60]). Among phylogenetic tools, the process of maximum parsimony is the one following Occam's razor (i.e. when multiple hypotheses can explain the same data, the simplest of those hypotheses is the one most likely to be true). The relevant issue to our discussion is that the principle of maximum parsimony works fairly well when reconstructing phylogenetic relationships of organisms, even when compared with methods using complex probabilistic models [61,62], suggesting that evolution commonly follows the shortest mutational path across species. Thus, that QW are more efficient than CRW at exploring evolutionary space may explain maximum parsimony's efficiency at phylogenetic reconstructions.

4.1.2. Epigenetics

This area of science investigates the regulatory mechanisms that during development lead to persistent and inducible heritable changes that do not affect the genetic composition of the DNA. Some of these changes can actually regulate the function of DNA without changing its base composition, via, for example, methyl groups [63]. Epigenetic inheritance refers to those phenotypic variations that do not depend on DNA sequence variations, and that can be transmitted across generations of individuals (soma-to-soma) and cell lines (i.e. cellular epigenetic inheritance); such processes can lead to soft inheritance [64]. There are four basic types of epigenetic inheritance. (i) Self-sustaining regulatory loops, where following the induction of gene activity, the gene's own product acts as a positive feedback regulator

maintaining gene activity across cell generations. (ii) Structural templating, where preexisting three-dimensional structures serve as models to build similar structures in the next generation of cells. (iii) Chromatin markings, where small chemical groups (e.g. methyl CH_3) bind to DNA, altering/controlling gene activity; they can segregate during DNA replication and be reconstructed in daughter DNA molecules. (iv) RNA-mediated inheritance, where silent transcription states are maintained by interactions between small RNA molecules and their complementary mRNA and DNA. These states can be transmitted to cells and organisms via an RNA replication system, also by having small RNAs modifying heritable chromatin marks, and by inducing heritable gene deletions [65] (see [66] for a gentle general introduction to epigenetics).

What is most relevant for the proposed framework is the fact that environmental factors (e.g. heat shock, starvation, chemicals, stress in general) can directly (germline) or indirectly (somatic alterations) induce developmental modifications via heritable epigenetic variations, which underlie developmental plasticity and canalization [64,67,68]. If we implement the n -dimensional network concept of [15] to an epigenome, we can obtain an epigenetic network on which the selective environment can induce state changes in the expression and functioning of genes via epigenetic marks [63] (see also [55]). Moreover, the response to the environment would be faster when fewer mutational or epimutational steps are required in reference to the selective environmental conditions (e.g. [69]), which may be more efficiently explored and found by QW. This last proposition can explain why in 'clonal' bacterial evolutionary experiments not all colonies respond at the same time to the same environmental challenge, some respond differently but with similar results and some do not respond at all during the length of the experiment (see figures 2 and 5; e.g. [37,69,70–72]). The outcome will depend on exactly the structure of the genotype or epigenotype network and where on the network evolution started during experiments.

4.1.3. Niche construction

This is another non-Darwinian process imposing novel challenges on organisms via changes generated on the environment by the same organisms [73]. In other words, changes imposed on the environment by species modify the adaptive landscape and the n -dimensional genotype network across generations. Such changes might produce environmental feedbacks on both the same organisms producing the change and indirectly on those other organisms under the influence of the novel environment. A novel environment will alter the probabilistic nature of the QW, changing the likelihood of evolutionary pathways (i.e. creating new evolutionary constraints), which according to our results would be better explored by the diverse behaviour of the QW than CRW.

The framework presented here provides a probabilistic process (via a quantum wave function) that might act as the mechanism for the evolutionary exploration of n -dimensional genotype networks within the constraints established by the available options (i.e. phenotypes). In this sense, our study complements the initial work of [7] and [8] by providing an evolutionary context (highly diverse and robust n -dimensional genotype networks), where a quantum wave

function is the mechanism of evolutionary exploration. The process still needs to be investigated in much larger n -dimensional genotype networks and also under open system scenarios, where the environment might influence system behaviour. Such analysis will determine environmental selection regimes for different genotypes of a genotype network (quantum superposition), which may allow a more efficient evolutionary exploration (e.g. [11,55]). Phenotypic options will be given by the current genomic context of the population (i.e. the n -dimensional genotype network), which are not necessarily better or best for the current conditions, but are most likely in accordance with current context (i.e. evolutionary constraints; see [74] for a probable example of this effect).

A way to prove our theory experimentally can be by using clonal bacterial colonies that start from different positions in the genotype network, in such a way that decoherence times can be measured under the influence of a novel environment (e.g. lactose); such times should be repeatable across experiments (figure 5). Modern -omics (e.g. genomics, transcriptomics) and biotechnology techniques can be used to construct specific bacterial lines for such experiments. In addition, it would be possible to analyse the epigenome of plants, which are the organisms where this type of evolutionary process is more common.

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Data accessibility. The Mathematica code and data used for simulations supporting results of this article are available upon request to htapia@uv.mx and are publicly stored as electronic supplementary material in figshare.com. Here is a link to all materials and results from the simulations in dropbox: <https://www.dropbox.com/sh/wnjh7pfanwb7o9e/AAASpCG-O9TIRZdncXwhmS0wa?dl=0>.

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