Quantum entanglement shared in hydrogen bonds
and its usage as a resource in molecular recognition

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Quantum tunneling events occurring through biochemical bonds are capable to generate quantum correlations between bonded systems, which in turn makes the conventional second law of thermodynamics approach insufficient to investigate these systems. This means that the utilization of these correlations in their biological functions could give an evolutionary advantage to biomolecules to an extent beyond the predictions of molecular biology that are generally based on the second law in its standard form. To explore this possibility, we first compare the tunneling assisted quantum entanglement shared in the ground states of covalent and hydrogen bonds. Only the latter appears to be useful from a quantum information point of view. Also, significant amounts of quantum entanglement can be found in the thermal state of hydrogen bond. Then, we focus on an illustrative example of ligand binding in which a receptor protein or an enzyme is restricted to recognize its ligands using the same set of proton-acceptors and donors residing on its binding site. In particular, we show that such a biomolecule can discriminate between \(3^n - 1\) agonist ligands if it uses the entanglement shared in \(n\) intermolecular hydrogen bonds as a resource in molecular recognition. Finally, we consider the molecular recognition events encountered in both the contemporary genetic machinery and its hypothetical primordial ancestor in pre-DNA world, and discuss whether there may have been a place for the utilization of quantum entanglement in the evolutionary history of this system.
I. INTRODUCTION

The conventional thermodynamics is based on the famous molecular chaos hypothesis, which does not allow any correlation between the atoms and molecules. The second law derived within this theory is fundamental to understanding the biochemistry of cellular processes. However, there is a tradeoff between correlation and entropy, due to which the second law, in its standard form, is insufficient in the presence of nonlocal correlations, e.g., initial quantum correlations may lead to anomalous heat flows from the cold to the hot systems. In this respect, an interesting question to ask is whether biological molecules can share quantum correlations, which in turn plays a key role in the cellular functions of these molecules beyond the conventional thermodynamics.

Quantum correlations can be generated by the electron and proton tunneling events occurring through the chemical bonds formed between biological molecules. In particular, a covalent bond is nothing but the correlated tunneling of two electrons between two atoms. Consider a single covalent bond formed between two arbitrary atoms labeled by X and Y. The ground state of this bond can be written as a coherent quantum superposition:

$$|X-Y\rangle = \alpha|X\rangle \otimes |Y\rangle + \beta|X\rangle \otimes |Y^+\rangle + \gamma|X^+\rangle \otimes |Y^-\rangle$$

where all the probability amplitudes depend on distance $$r \equiv d(X, Y)$$ and obeys normalization conditions $$|\alpha|^2 + |\beta|^2 + |\gamma|^2 = 1$$, the black and gray dots stand for the electrons participating in the chemical bond, the former term $$|X-Y\rangle$$ represents the share of two electrons in the bonding molecular orbital $$\sigma_{X-Y}$$ and the subsequent two terms are responsible for the partial ionic character of the bond.

When the second atom labeled by Y is a hydrogen (H), the last ionic term in (1) can be ignored because of the weak electron affinity of this atom. The X–H molecule is then able to form a weak chemical bond with a second electronegative atom, known as hydrogen bond (H-bond). The atom which is initially bonded to H is called proton-donor, while the second atom is called proton-acceptor. Either the electrons of the proton-acceptor or the proton of the H atom can tunnel back and forth between the proton-donor and -acceptor.

Consider a H-bond between two arbitrary atoms $$X_1$$ and $$X_2$$. This bond is defined by means of the geometric parameters $$r(t) \equiv d(X_1, H)$$, $$R(t) \equiv d(X_1, X_2)$$, $$\phi(t) \equiv \angle X_1X_2H$$. To minimize the overall energy, the amounts of neutral and ionic contributions to the ground state of the $$X_1-H$$ bond are initially rearranged in the presence of $$X_2$$ as follows:

$$|\psi(t) = 0, R = \infty\rangle = \left(\alpha(r)|X_1\rangle \otimes |H\rangle + \beta(r)|X_1\rangle \otimes |H^+\rangle\right) \otimes |\cdot X_2\rangle$$

$$\rightarrow \left(\alpha'(r, R, \phi)|X_1\rangle \otimes |H\rangle + \beta'(r, R, \phi)|X_1\rangle \otimes |H^+\rangle\right) \otimes |\cdot X_2\rangle$$

$$= \alpha'(r, R, \phi)|X_1\rangle \otimes |\cdot X_2\rangle + \beta'(r, R, \phi)|X_1\rangle \otimes |H^+\rangle \otimes |\cdot X_2\rangle \equiv |X_1-H \equiv X_2\rangle$$

where $$r(t) > r(0)$$ and $$|\alpha'(r, R, \phi)|^2 < |\alpha(r)|^2$$ for $$t > 0$$ in general.

As the changes in the amplitudes described above are only induced by electrostatic interactions, the state transition from (2) to (3) is completely classical and is expected to occur for every proton-donor and -acceptor pair. Besides this, the electron lone pair orbital of the proton-acceptor and the unoccupied antibonding orbital of the proton-donating bond $$\sigma_{X_1-H}^*$$ may overlap in the ground state of the whole system, which in turn results in a charge transfer from the lone pair orbital to $$\sigma_{X_1-H}^*$$ in the form of electron tunneling. This electron delocalization occurring in the ground state not only weakens and elongates $$X_1-H$$ bond, but also gives a partially covalent character to the interaction $$H \equiv X_2$$:

$$|X_1-H \equiv X_2\rangle \rightarrow \alpha_-|X_1\rangle \otimes |\cdot X_2\rangle + \beta_-|X_1\rangle \otimes |H^-\rangle + \gamma_-|X_1\rangle \otimes |H^+\rangle \otimes |\cdot X_2\rangle$$

where $$|\alpha_-|^2 + |\beta_-|^2 + |\gamma_-|^2 = 1$$. Here, we omit the dependence of amplitudes on the geometric parameters for the sake of simplicity of notation and depict the presence of an electron in the antibonding orbital $$\sigma_{X_1-H}^*$$ by a dot above a second line between $$X_1$$ and H.

Such orbital interactions are of importance for many H-bonded systems in biology as their absence may lead to compression of the $$X_1-H$$ bond rather than its expected elongation. As an example, the covalent contribution to attractive energy may be comparable to the electrostatic contribution for interbase H-bonds holding two strands of DNA together. That is to say, the electron delocalization through H-bonds may be vital to the stability of Watson-Crick base pairing. However, it is still too early to reach a consensus on this matter as the results depend on which quantum chemical model is in use.

The extent of the covalency of H-bonds is not limited to the lone pair electrons of the proton-acceptor. The proton which constitutes the nucleus of the H atom is also likely to be delocalized between $$X_1$$ and $$X_2$$ due to the orbital...
interactions in the ground state \([1]:\)

\[|X_1 - H \equiv X_2 \rangle \rightarrow \alpha_+ |X_1 \rightarrow H \rangle \otimes |· - X_2 \rangle + \delta_+ (|X_1 \cdot \rangle \otimes |(H - X_2)^+ \rangle + \beta_+ (|X_1 \cdot \rangle \otimes H^+ , · - X_2 \rangle \equiv |X_1 - (H - X_2) \rangle, \tag{5}\]

where \(|\alpha_+|^2 + |\delta_+|^2 + |\beta_+|^2 = 1\). This is observed especially in so called low barrier H-bonds (LBHBs) and short and strong H-bonds (SSHBs). The existence of such bonds in enzymes and their functional role in bioanalysis are still controversial \([\text{17-22}]\). Additionally, the nuclei of H atoms are also likely to tunnel through the interbase H-bonds \([\text{23}]\)

In this paper, we take into account the quantum entanglement generated by the electron and proton tunneling events occurring through H-bonds in a hypothetical molecular recognition scenario in which there is a restriction on the number of intermolecular H-bonds. This enables us to discuss the possible roles of quantum tunneling in ligand discrimination within the frameworks of quantum information theory and thermodynamics where the correlations are routinely regarded as a resource for specific tasks. Before doing so, we examine the usefulness of quantum entanglement shared between covalent and H-bonded atoms in the following section.

II. QUANTUM ENTANGLEMENT GENERATED THROUGH CHEMICAL BONDS:
COVALENT VS HYDROGEN BONDS

To provide perceptive insights into the correlations generated by the motion of electrons or protons in a chemical bond, we will reduce the complexity by focusing only on the state of particles participating in the bond in what follows. Furthermore, we will neglect the spin degrees of freedom to give prominence to the particle positions. Finally, we will quantify the quantum correlations found in a generic bipartite state \(\rho\) in terms of its entanglement of formation, a measure defined as \([33]\)

\[E_F[\rho] = \min \left( \sum_i p_i E_F[|\psi_i\rangle\langle\psi_i|] \right), \tag{6}\]

where the minimum is taken over all possible pure state decompositions that realize \(\rho = \sum_i p_i |\psi_i\rangle\langle\psi_i|\), \(E_F\) is the entropy of entanglement that equals to \(E_F[\rho] = S[\rho_{1(2)}] = (S \circ \text{tr}_{2(1)})[\rho]\), \(S\) is the von Neumann entropy defined as \(S[\rho] = -\text{tr}[\rho \log_2 \rho]\), and \(\text{tr}_{2(1)}\) is the partial trace over the degrees of freedom of the second (first) subsystem.

In this respect, one natural choice is to describe the covalent bond based on a one-qubit representation for the state of an electron such that when an electron participating in the bond resides in the atomic orbital of X (Y), it is described by \(|0\rangle\) \(|1\rangle\). The generic state given in \([\text{33}]\) then becomes:

\[|X - Y\rangle = a|01\rangle_{12} + b|10\rangle_{12} + \beta|00\rangle_{12} + \gamma|11\rangle_{12}, \tag{7}\]

where the electrons depicted by black and gray dots in \([\text{33}]\) are labeled respectively by 1 and 2. However, there is a flaw in this description because of the indistinguishability of the electrons. Consider the pure covalent bond corresponding to \(a|01\rangle_{12} + b|10\rangle_{12}\). This two-qubit state is entangled for all nonzero values of \(a\) and \(b\), i.e., \(E_F = -|a|^2 \log_2 |a|^2 - |b|^2 \log_2 |b|^2 > 0\) when \(0 < |a|^2 < 1\) and \(0 < |b|^2 < 1\). However, as the two electrons are identical, it is not possible to discriminate between the states \(|01\rangle_{12}\) and \(|10\rangle_{12}\). Hence, although their coherent superposition originates from the correlated delocalization of the electrons, it does not possess any quantum entanglement which is useful from a quantum information and thermodynamics point of view.

Another problem of this description of the covalent bond is that the two-qubit state \([\text{33}]\) can be either separable or entangled depending not only on the values of the amplitudes, but also their signs. For example, the values of \(a = b\alpha = b = \gamma = 0.5\), which correspond to 50 percent ionic character in the ground state of the molecule, give zero entanglement as \(|X - Y\rangle = 1/2 (|01\rangle + |11\rangle) \otimes (|02\rangle + |12\rangle)\). When one of the amplitudes changes its sign, e.g., \(\beta\) becomes \(-0.5\), neither the total amount of ionic character of the bond nor the contribution of each ionic structure to the ground state of the molecule changes. However, \([\text{33}]\) turns out to be an entangled state in this case as it cannot be written in the form of \((\lambda_1 |01\rangle + \lambda_2 |11\rangle) \otimes (\lambda_3 |02\rangle + \lambda_4 |12\rangle)\) anymore, where \(\lambda_j\) are proper amplitudes obeying local normalization conditions. Furthermore, the entanglement between the electrons is found to be maximal as reduced states of \([\text{33}]\) are maximally mixed for these values, i.e., \(\rho_{1(2)} = 1/2 (|0\rangle \langle 0| + |1\rangle \langle 1|)\) and \(E_F [|X - Y\rangle \langle X - Y|] = 1\). When a second sign flip occurs, e.g., \(\gamma\) also becomes \(-0.5\), probability of each ionic structure still remains at 0.25, but the two electrons get disentangled once again: \(|X - Y\rangle = 1/2 (|01\rangle - |11\rangle) \otimes (-|02\rangle + |12\rangle)\). Hence, changes in the amplitudes which do not affect the partial ionic character of the bond can alter the amount of quantum entanglement generated through the bond dramatically from 0 to 1 or vice versa according to this representation.
To overcome these two flaws, it is better to move on to a one-qutrit representation for the state of each atomic orbital such that an orbital participating in the bond is regarded to exist in state $|n\rangle$ when it is occupied by $n = \{0, 1, 2\}$ electrons. The generic state given in (8) then becomes:

$$|X - Y\rangle = \alpha|11\rangle_{XY} + \beta|20\rangle_{XY} + \gamma|02\rangle_{XY},$$

(8)

where the subscript $X$ ($Y$) stands for the atomic orbital of $X$ ($Y$). This two-qutrit state do not possess any entanglement in the pure covalent case and it is entangled whenever the bond has a partial ionic character, i.e., $E_{F} [\langle X - Y\rangle_{XY} |X - Y\rangle_{XY}] > 0$ only for nonzero values of $\beta$ and/or $\gamma$. That is to say, the electron tunneling is able to create useful entanglement as long as the ionic character of the covalent bond does not vanish.

Let us start discussing the correlations in H-bonds first in this context. To do so, we consider the ground state of a classical H-bond depicted as $|X_{1} - H \equiv X_{2}\rangle$ in (3) and rewrite it using the one-qutrit representation of atomic orbitals:

$$|\psi(t_{t} = 0, R_{t} = \infty)\rangle = (\alpha(r)|11\rangle_{X_{1}H} + \beta(r)|20\rangle_{X_{1}H}) \otimes |2\rangle_{X_{2}}$$

$$\quad \rightarrow \alpha'(r, R, \phi)|11\rangle_{X_{1}H} \otimes |2\rangle_{X_{2}} + \beta'(r, R, \phi)|20\rangle_{X_{1}H} \otimes |2\rangle_{X_{2}} \equiv |X_{1} - H \equiv X_{2}\rangle.$$

(9)

Since $|\beta'(r, R, \phi)|^{2} > |\beta(r)|^{2}$ for $t > 0$, the amount of ionic character of the $X_{1} - H$ bond increases due to the electrostatic interactions with the proton-acceptor $X_{2}$, so does the amount of useful entanglement generated by electron tunneling between $X_{1}$ and $H$. Hence, although any fresh entanglement cannot be created in this type of H-bonds, the entanglement existing in covalent bonds can be enhanced.

Now, we can move on to the relation between the covalency of H-bonds and the entanglement in them. To refine this relation, we first neglect the ionic character of the $X_{1} - H$ bond taking $\beta_{-}$ in (8) to be zero. In this way, we eliminate the entanglement generated by this single covalent bond. We then extend the one-qutrit representation to include the molecular orbitals as well. This enables us to rewrite the ground state $|(X_{1} - H) - X_{2}\rangle$ in (4) simply as:

$$|X_{1} - H \equiv X_{2}\rangle = |2\rangle_{\sigma^{\ast}} \otimes |2\rangle_{X_{2}}$$

$$\rightarrow |2\rangle_{\sigma} \otimes (\alpha_{-}|02\rangle_{\sigma^{\ast}X_{2}} + \delta_{-}|11\rangle_{\sigma^{\ast}X_{2}}) \equiv |(X_{1} - H) - X_{2}\rangle,$$

(10)

where $\sigma$ and $\sigma^{\ast}$ stand respectively for the bonding molecular orbital $\sigma_{X_{1} - H}$ and the antibonding molecular orbital $\sigma_{X_{1} - H}^{\ast}$.

The two-qutrit state given in the parenthesis above is entangled unless $\delta_{-}$ is equal to zero, which corresponds to vanishing charge transfer in the form of electron delocalization. This means that the covalent character of a H-bond implies the formation of useful entanglement between the H-bonded atoms. Note that the entanglement generated by electron delocalization between two covalent-bonded atoms conversely requires a partial ionic character and is useless otherwise.

Finally, we take into account the quantum entanglement in the H-bonds involving proton delocalization. To eliminate the entanglement generated by the single covalent bonds as before, we neglect their ionic character taking $\beta_{+}$ in (3) to be zero. We then represent the state of the atom $X_{2}$ by $|1\rangle$ if it is covalently bonded to the hydrogen and by $|0\rangle$ otherwise. This one-qutrit representation is in line with the previous treatment of the atomic/molecular orbital occupancy using a one-qutrit representation and allow us to rewrite the ground state in (3) as:

$$|X_{1} - H \equiv X_{2}\rangle = |10\rangle_{X_{1}X_{2}} \rightarrow \alpha_{+}|10\rangle_{X_{1}X_{2}} + \delta_{+}|01\rangle_{X_{1}X_{2}} \equiv |X_{1} - (H) - X_{2}\rangle.$$

(11)

The amount of the entanglement found in this two-qubit state is exactly the same as the one found in the three-qutrit state given in (8) when $\delta_{+} = \delta_{-}$, i.e., $E_{F} [\langle X_{1} - (H) - X_{2}\rangle |X_{1} - (H) - X_{2}\rangle] = E_{F} [\langle (X_{1} - H) - X_{2}\rangle |(X_{1} - H) - X_{2}\rangle] = -|\delta_{+}|^{2} \log_{2} |\delta_{+}|^{2} - (1 - |\delta_{+}|^{2}) \log_{2} (1 - |\delta_{+}|^{2})$. The only difference between these two entanglements is that the former is a correlation directly between $X_{1}$ and $X_{2}$ atoms, while the latter is a correlation actually between $X_{1} - H$ molecule and $X_{2}$ atom.

We have neglected the partial ionic character of the $X_{1} - H$ bond to investigate the quantum entanglement that originates in a H-bonded system from tunneling of either the electrons of $X_{2}$ atom or the proton of the $H$ atom. Although the entanglement generated in this way was found to be useful from a quantum information and thermodynamics point of view, its amount obviously decreases with the raising ionic character of proton-donating covalent bond. Remark that, contrarily to H-bonds, quantum tunneling of the bonding electrons was shown to be incapable of creating useful quantum entanglement in covalent bonds. Instead, covalent bonds were found to require a particular amount of ionic character to possess a useful quantum entanglement between their bonded atoms. Hence, either the tunneling of bonding particles or the ionic character of the chemical bond has opposite effects on the amount of useful entanglement shared in covalent and H-bonds.
III. ENVIRONMENTAL EFFECTS ON CORRELATIONS: THERMALIZATION & DECOHERENCE

Here and in the following, we will describe the many-particle ground state of a H-bonded system using a unified representation as follows:

$$\rho_{\text{th}} = \sum_{m=1}^{N} e^{-\beta \epsilon_m} \frac{1}{Z} |\epsilon_m\rangle \langle \epsilon_m|,$$

where $N$ is the total number of energy eigenstates, $\beta$ is the inverse temperature of the environment that equals to $1/(k_B T)$, and $Z$ is the partition function that can be written as $\sum_m e^{-\beta \epsilon_m}$. All the excited states $|\epsilon_m\rangle$ should be orthogonal to the ground state due to the Hermiticity of the many-particle Hamiltonian, which in turn opens up the possibility that some of the excited states living inside the subspace $H_{123}$ spanned by $\{\psi_1, |\psi_2\rangle, |\psi_3\rangle\}$ can be also entangled to the same extent as the ground state. This may provide a significant amount of entanglement in the thermal state given in (13).

To illustrate this argument in detail, suppose that $\alpha_\pm = \beta_\pm = \delta_\pm = 1/\sqrt{3}$ in (12) and there are only two excited states living inside $H_{123}$ as $|\epsilon_2\rangle = (|\psi_1\rangle + |\psi_2\rangle - 2|\psi_3\rangle)/\sqrt{6}$ and $|\epsilon_3\rangle = (|\psi_1\rangle - |\psi_2\rangle)/\sqrt{2}$. Using the representation introduced just before (13), which gives $|\psi_1\rangle = |10\rangle$, $|\psi_2\rangle = |01\rangle$, and $|\psi_3\rangle = |00\rangle$, the entanglement of formation is found to be 0.550048, 0.187299, and 1 respectively for $|\epsilon_1\rangle$, $|\epsilon_2\rangle$, and $|\epsilon_3\rangle$. The thermal state is then likely to possess a non-negligible amount of entanglement for several values of the Boltzmann factors $\{e^{-\beta \epsilon_m}/Z\}$, e.g., $E_F[\rho_{\text{th}}]$ equals to 0.283771 when $\{\epsilon_1, \epsilon_2, \epsilon_3\}$ equals to $\{0.7, 0.2, 0.1\}$.

However, the effect of its environment on a quantum system is not limited to the thermalization, which originates from the exchange of energy between the system and environment. In addition to this, information can be also exchanged so that leakage of system’s information into its environment results in decoherence, which washes out all the entanglement generated inside the system in the long-time limit. This corresponds to disappearance of the all non-diagonal elements in the density matrix which describes state of the system, e.g., $\rho_{\text{th}} \rightarrow \rho_{d} = (22|00\rangle \langle 00| + 19|01\rangle \langle 01| + 19|10\rangle \langle 10|)/60$ for the amplitudes and Boltzmann factors given in the previous paragraph and this diagonal state has actually zero entanglement of formation.

IV. ENTANGLEMENT AS A RESOURCE IN MOLECULAR RECOGNITION

Ligand binding typically occurs by weak intermolecular interactions such as H-bonds, and constitutes one of the major biochemical functions of proteins. Hence, we will focus on the quantum entanglement shared between H-bonded molecules in an illustrative example of ligand binding and investigate the possibility of its usage as a resource in what follows.

Consider a molecule, a receptor protein or an enzyme, which is responsible for the recognition of two different ligands. Assume that this molecule, say that the molecule $A$, binds each of its ligands through a single H-bond and participates in either intermolecular H-bond with the same proton-acceptor atom/molecule $X_1$ residing on its binding site. To challenge $A$ a bit more, also assume that these two ligands, the molecules $B$ and $C$, share not only a common molecular shape, but also a similar hydrophobicity and charge distributions such that even their proton-donating covalent bonds possess comparable amounts of ionic characters during the interaction with $X_1$. However, allow a difference in the extent of electron/proton delocalization events occurring in the two single H-bonds. Can the molecule $A$ distinguish one ligand from the other and produces a different agonist response upon binding to each of them under such circumstances?

The assumptions given above make binding affinities very close to each other in both cases, which in turn puts a strain on the distinguishability of the ligands unless $A$ is somehow capable of identifying the entanglements shared in the two intermolecular H-bonds. To explore this capability within the framework of quantum information theory, we
will take into account the following states

\[ |X_B - (H) - X_1\rangle = \frac{1}{\sqrt{3}}(|\psi_1\rangle + |\psi_2\rangle + |\psi_3\rangle), \]  
\[ |X_C - (H) - X_1\rangle = \frac{1}{\sqrt{6}}(|\psi_1\rangle - 2|\psi_2\rangle + |\psi_3\rangle), \]

by which it is provided that i) ionic contribution to the proton-donating covalent bond is exactly the same as neutral contribution in each intermolecular H-bond, and ii) rate of back and forth proton tunneling between the proton-acceptor and -donor is doubled in the second H-bond when compared to the first H-bond. Note that in spite of this difference in the tunneling rates, the amounts of entanglement shared in these two bonds are equal, i.e., \( E_F [\langle X_B - (H) - X_1 \rangle \langle X_B - (H) - X_1 \rangle^\dagger] = E_F [\langle X_C - (H) - X_1 \rangle \langle X_C - (H) - X_1 \rangle^\dagger] = 0.550048. \)

To perform its biochemical function successfully, the molecule \( A \) is expected to undergo a different conformational transition depending on to which ligand it binds. To do so, it should first single the states (14) and (15) out from the other states living inside \( \mathcal{H}_{123} \) and then discriminate between them. As these two states are orthogonal to each other, they are physically distinguishable. However, \( A \) is able to access the information in them locally, i.e., the reduced state of \( X_1 \) equals to \( \langle 2 | 0 \rangle \langle 0 | + \langle 2 | 0 \rangle \langle 1 | + \langle 1 | 0 \rangle \langle 1 | + \langle 1 | 1 \rangle \rangle / 3 \) in the joint system \( X_B X_1 \), while it equals to \( \langle 5 | 0 \rangle \langle 0 | + \langle 0 | 1 \rangle \langle 1 | + \langle 1 | 0 \rangle \langle 1 | + \langle 1 | 1 \rangle \rangle / 6 \) in the joint system \( X_C X_1 \). These two density matrices are not orthogonal to each other, and so they are not perfectly distinguishable. Moreover, there are various states living inside \( \mathcal{H}_{123} \) which have the same reduced states with either (14) or (15) and some of them are even not entangled.

Despite the fact that the molecule \( A \) cannot recognize the entanglement found in a H-bond formed with another molecule, it can teleport this entanglement into one of its intramolecular H-bonds by means of local operations on each molecule and classical correlations between them. In this respect, imagine that there is a proton-donating \( X_2 - H \) bond in the close neighborhood of \( X_1 \) within the binding site of \( A \), but the ground state conformation of \( A \) does not allow any orbital interaction between \( X_1 \) and \( X_2 \), e.g., joint state of these atoms/molecules in the ground state conformation \( \chi_1 \) equals to

\[ |X_2 - H \| X_1\rangle = |\epsilon_1\rangle_{X_2 X_1} \equiv \frac{1}{\sqrt{2}}(|\psi_1\rangle - |\psi_3\rangle). \]

On the contrary, assume that the two lowest excited state conformations of \( A \), \( \chi_2 \) and \( \chi_3 \), switch on the orbital interaction between \( X_1 \) and \( X_2 \) such that they stabilize the intramolecular H-bond in the states which are exactly matching up with (14) and (15) respectively as below:

\[ |X_2 - H \| X_1\rangle \xrightarrow{X_2} |\epsilon_2\rangle_{X_2 X_1} \equiv \frac{1}{\sqrt{3}}(|\psi_1\rangle + |\psi_2\rangle + |\psi_3\rangle), \]  
\[ |X_2 - H \| X_1\rangle \xrightarrow{X_3} |\epsilon_3\rangle_{X_2 X_1} \equiv \frac{1}{\sqrt{6}}(|\psi_1\rangle - 2|\psi_2\rangle + |\psi_3\rangle). \]

In a sense, the conformation of \( A \) is regarded to continuously monitor the state of joint \( X_2 X_1 \) system such that when \( A \) is in a particular conformation \( \chi_j \), these H-bonded atoms are enforced to be in the state \( |\epsilon_j\rangle \). This kind of conditional dynamics can be described by a unitary operation defined as:

\[ U_A (|\psi(t_i)\rangle_{X_2 X_1} \otimes |\phi(t_i)\rangle_{\chi}) = \sum_{j=1}^{3} (M_j |\psi(t_i)\rangle_{X_2 X_1} \otimes |\epsilon_j\rangle), \]

where \( |\phi(t_i)\rangle_{\chi} \) is the initial conformational state of \( A \), \( M_j = |\epsilon_j\rangle_{X_2 X_1} \langle \epsilon_j| \) and \( \langle \epsilon_j| \chi_j \rangle = \delta_{jj'} \). Note that reduced dynamics of the joint \( X_2 X_1 \) system is nothing but a complete measurement since \( \sum_{j} M_j^\dagger M_j \) equals to \( I_{123} \), the identity operator acting on \( \mathcal{H}_{123} \).

The biochemical transformations starting upon ligand binding in the molecule \( A \) can then be described as a kind of entanglement swapping \( \boxed{[3] \quad [33]} \), a key element of various schemes in quantum information and quantum communication based on the extension of quantum teleportation \( \boxed{[24]} \), as follows. After forming an intermolecular H-bond with a molecule \( N \), \( A \) tries to swap the partner of \( X_1 \) in this bond with its atom \( X_2 \) using a measurement on the partner atom \( X_N \) followed by some operations on the joint \( X_N X_1 \) system that are classically correlated with the measurement outcome (see Appendix for the details). In the case of binding to the ligand \( B \) (\( C \)), perfect swapping of the entangled partner of \( X_1 \) brings the joint state of \( X_2 \) and \( X_1 \) into the eigenstate \( |\epsilon_2\rangle \) (\( |\epsilon_3\rangle \)) at time \( t_i \), which demands an accompanying conformational transition from \( \chi_1 \) to \( \chi_2 \) (\( \chi_3 \)) according to (13). Conversely, when the bonded molecule is neither \( B \) nor \( C \), state of the intramolecular H-bond is not likely to match up with one of the eigenstates of joint
the molecule \( A \) in the scope of the present paper. Each of bonded atoms which mathematically corresponds to a quantum measurement. However, by doing so, we do not chemical bonds (either in itself or in its ligands) to such an extent that it can impose a strict control on the state of a molecule different than \( B \) or \( C \). As an example, imagine an antagonist ligand \( D \), which forms the following H-bond with the molecule \( A \):

\[
|X_D-(H)-X_1\rangle = \frac{1}{\sqrt{6}}(|\psi_1\rangle + 2|\psi_2\rangle + |\psi_3\rangle).
\]

As it possesses not only an identical ionic character, but also completely the same tunneling probability with the molecule \( C \), the molecule \( D \) mimics \( C \) unless \( A \) benefits from the entanglement swapping to identify the bonded molecule. In this case, the molecule \( A \) is expected to reach the state \((2\sqrt{2}|\epsilon_2\rangle X_2 X_1 \otimes |\chi_3\rangle - |\epsilon_3\rangle X_2 X_1 \otimes |\chi_3\rangle)/3\) at the end of a molecular recognition process based on the entanglement swapping. This corresponds to a quantum coherent superposition of the whole molecule \( A \), which is highly improbable under the influence of quantum decoherence arising from the interaction with the cellular environment. Hence, \( D \) fails in its attempt to trigger a conformational change in the molecule \( A \), and the molecular recognition breaks down.

We have taken into account the proton delocalization in ligand-protein H-bonds so far, but note that our conclusions on the possibility of the usage of entanglement as a resource in ligand recognition also holds when we consider the electron delocalization in these bonds.

**V. IS THERE A ROOM FOR QUANTUM MEASUREMENT IN BIOLOGY?**

The molecule \( A \) appears to be able to make quantum measurements either on itself or on its ligands in different steps of the molecular recognition scenario described above. However, there is a lack of consensus on how the quantum measurement affects the state of a simple physical system, which is reflected by the wide range of interpretations of quantum mechanics from Copenhagen interpretation to many-worlds interpretation. In this respect, we should be careful about what we mean by a quantum measurement within the framework of molecular biology.

The reduced dynamics of the joint \( X_2 X_1 \) system during the unitary evolution \( U_A \) given in (19) is mathematically equivalent to a joint measurement in the basis of \( \{|\epsilon_j\rangle\} \) as mentioned before. This reduced dynamics actually emerges from \( U_A \) as a consequence of the elimination of conformational degrees of freedom of the molecule. That is, the state of H-bond found between the atoms \( X_2 \) and \( X_1 \) is measured, in a sense, by means of the state of conformation in the course of closed system dynamics of the molecule. Hence, this measurement can be regarded as an influence of the conformational dynamics on the H-bond under consideration.

Besides this, initialization of the teleportation of intermolecular entanglement shared in \( X_N-(H)-X_1 \) bond to the intramolecular \( X_2-H=X_1 \) bond requires a measurement on \( X_N \) in the basis of \( \{\lambda_1|1\rangle + \lambda_2|0\rangle, \lambda_2^*|1\rangle - \lambda_1^*|0\rangle\} \) (see Appendix for the details). Note that the probability amplitudes \( \lambda_1 \) and \( \lambda_2 \) obey the normalization condition \( |\lambda_1|^2 + |\lambda_2|^2 = 1 \), while the computational basis states \( |1\rangle \) and \( |0\rangle \) stand for respectively \( |X_N=-H\rangle \) and \( |(X_N-\cdot)\rangle \) (C-H\(^+\)). On that account, this measurement operationally enforces the \( X_N-H \) covalent bond to display a particular amount of ionic character at either \((1 - |\lambda_1|^2) \times 100 \) or \(|\lambda_1|^2 \times 100 \) percentage. It may be physically impossible for a number of proton-donors to display such an ionic character, which in turn halts the entanglement swapping at the very beginning for some ligands. Hence, the initial measurement on \( X_N \) may serve as a first-line discrimination mechanism for the molecule \( A \) to single out the ligands having the right amounts of ionic character from the others.

On the other hand, entanglement swapping between \( X_N-(H)-X_1 \) and \( X_2-H=X_1 \) bonds does not need any further quantum operation on the ligand molecule. We can then reasonably assume that the basis states of the measurement under consideration coincide with the states of molecules \( B \) and \( C \) in the absence of any interaction with \( A \) so that the measurement projects the two agonist ligands into their initial states. Actually, reorganization of the binding site of \( A \) should be capable to provide such a charge stabilization on \( X_N \). Hence, this measurement can be regarded as a backwash effect of the conformational dynamics of the molecule \( A \) on the proton-donating \( X_N-H \) covalent bond.

In this way, we argue that the conformational change of a receptor protein or an enzyme may affect the intramolecular chemical bonds (either in itself or in its ligands) to such an extent that it can impose a strict control on the state of bonded atoms which mathematically corresponds to a quantum measurement. However, by doing so, we do not interpret any biological molecule or its environment as an observer or measurement device. As a matter of fact, each measurement performed on the quantum state of covalent or H-bonded atoms in our molecular recognition scenario can be characterized as an emergent property of the complex chemical interactions occurring in vivo, which are outside the scope of the present paper.
VI. OPTIMUM NUMBER OF HYDROGEN BONDS IN A MOLECULAR SEARCH

We have proposed a molecular recognition scenario in which a receptor protein or an enzyme can, at least in principle, harvest the entanglement shared in an intermolecular H-bond to generate a physiological response in the form of conformational change. The number of agonist ligands discriminated by a single H-bond was 2 in this scenario. To discuss the efficiency of the recognition process under consideration, we will extend it to the case of more than two agonist ligands discriminated by multiple H-bonds.

In this respect, we assume that the molecule $A$ is responsible for the recognition of $N$ different ligands using the same set of proton-acceptors and donors $\{X^k_j\}$ residing on its binding site. We let $n \geq 2$ of the intermolecular H-bonds formed between $(X^k_j, X^k_{j'})$ pairs to have partially covalent character, but do not allow any correlation between them. If $A$ is capable to teleport the entanglement shared in each of these $n$ intermolecular H-bonds to one of its distinct intramolecular H-bonds, it can then discriminate between $N = 3^n - 1$ ligands when the unitary evolution $U_A$ given in (19) is extended into:

$$U_A \left( \bigotimes_{k=1}^n |\psi(t_i)\rangle_{X^k_jX_k^j} \otimes |\phi(t_i)\rangle_X \right) = \sum_{j=1}^3 \bigotimes_{k=1}^n (M^k_j|\psi(t_i)\rangle_{X^k_jX_k^j}) \otimes |\chi_{j+3(k-1)}\rangle,$$

where $M^k_j = |\epsilon^k_j\rangle\langle \epsilon^j_k|X^k_jX_k^j|$ and $\langle \chi_{j+3(k-1)}|X^k_j+3(k'-1)\rangle = \delta_{j,j'} \delta_{kk'}$. That is to say that, formation of 2 intermolecular H-bonds involving proton or electron delocalization is sufficient to single out 8 agonist ligands from an infinite number of antagonist ligands. Addition of one more partially covalent H-bond increases the maximum number of discernible ligands from 8 to 26. This corresponds to an enormously high efficiency. Let us compare it to the efficiency of genetic machinery, which is expected to operate quite accurate and very fast molecular recognition events.

First and foremost, DNA and RNA molecules that carry the genetic information inside a cell are made up from only 4 of the tens of nucleobases. A new DNA (RNA) strand is synthesized by one or more DNA (RNA) polymerase enzymes by means of a template consisting of a pre-existing polynucleotide strand complementary to it in the sense of Watson-Crick base pairing. During the course of this process, a given polymerase may recognize its 4 distinct nucleobase ligands in the template over one of the three different edges on nucleobases, namely Watson-Crick, Hoogsten, and sugar edges appearing respectively at base pairing, major groove and minor groove sides of the double-helical structure of the nucleic acid. Such an enzyme can form at most 2 or 3 H-bonds with its ligands if the molecular recognition occurs over the Watson-Crick edges, whereas no more than 1 H-bond can be formed during the protein-ligand interactions in the minor groove. However, polymerase enzymes are not restricted to participate in their intermolecular H-bonds with the same set of proton-acceptors and donors as opposed to the spurious molecule $A$, which requires $n \approx 1.47$ partially covalent H-bonds to distinguish 4 ligands in our scenario.

Besides this, proteins that are responsible for various biological functions exerted inside a cell are made up from only 20 of the more than 700 amino acids. There is one special aminocyl-tRNA synthetase enzyme (aaRS) for each of these 20 amino acids (with some exceptions) in bacteria. In eukaryotes, cytoplasmic aaRSs and mitochondrial aaRSs are different from each other, but none of them is generally able to be loaded by more than one particular amino acid as well. These enzymes transfer their cognate amino acids onto acceptor stems of their cognate tRNA molecules in the first step of protein synthesis. To do so, a given aaRS should single out 1, 2, 4, or 6 tRNA molecules from the 64 possibilities depending on to which amino acid it is assigned. These molecular recognition processes are generally determined by only a couple of nucleotides from among the first four nucleobase pairs at the acceptor stem together with the preceding unpaired nucleobase at position 73 according to the conventional tRNA numbering system [37, 38]. Additionally, aaRSs are divided into two classes each of which contains enzymes specific for 10 of the amino acids and has a distinct activity mechanisms such that class I enzymes dock onto the minor groove side of the acceptor stem, whereas class II enzymes approach the helical oligonucleotides from the major groove side [38]. Hence, an aaRS is capable to form a few intermolecular H-bonds to discriminate its tRNA ligands against all the others. However, likewise the polymerase enzymes, these synthetase enzymes also do not form their intermolecular H-bonds over the same set of proton-acceptors and donors. On the contrary, the spurious molecule $A$ proposed in our scenario distinguishes 6 ligands by only $n \approx 1.77$ partially covalent H-bonds associated with the same proton-acceptors and donors residing its binding site.

VII. A DISCUSSION ON THE PRIMORDIAL SYNTHETASES OF THE PRE-DNA WORLD

aaRSs are the vital elements of protein synthesis as they provide a physical basis for the connection between the receipt encoded by nucleic acids and the product made by amino acids. Note that they are also products of the protein synthesis itself. As a result of this, evolutionary history of these enzymes and their ligands has received a
lot of attention in the literature. On the one hand, the 3-dimensional region of tRNA acceptor stems recognized by aaRSs is suggested to constitute an operational RNA code, which may have been a predecessor of the contemporary genetic code in RNA world [37]. On the other hand, origin of aaRSs is widely dated back to before the split of three kingdoms of life known as Bacteria, Archea, and Eucarya [38]. Since no structural or functional resemblance has been observed between the two aaRS classes, but conserved active site domains in all members of a given class have familiar structure and sequence motifs [37–39], each class may have evolved from a different ancestor.

Nonconservative domains of the modern aaRSs were probably added to their ancestors later in their evolution and intertwined with the emergence of the anticodon domain in tRNA ligands [27]. Hence, primordial synthetases of the pre-DNA world may have been smaller proteins having less atoms in their active sites. Also, it is trivial that they were likely to be responsible for the discrimination of too many ligands when compared to modern aaRSs, e.g., they may have not specialized for only one amino acid and their nucleotide ligands may have not been limited to tRNAs, but may have also included some cellular RNAs. In a sense, progenitors of modern aaRSs may have been restricted in recognizing their ligands to the same extent as the spurious molecule $A$ is restricted in our scenario. On that account, these ancient enzymes may have utilized the quantum entanglement shared in intermolecular H-bonds in a way similar to that $A$ does to change its configuration upon binding to an agonist ligand. That is, quantum entanglement may have played a pivotal role in the emergence of genetic machinery when the first enzymes were discriminating more nucleotides using less H-bonds.

VIII. CONCLUSIONS

Using the tools of quantum information theory, we approached the back and forth quantum tunneling events taking place between chemically bonded atoms. We showed that tunneling of an electron pair that defines a covalent bond cannot generate a useful quantum entanglement because of the indistinguishability of the electrons. However, if a covalent bond possesses a particular amount of ionic character, then it can acquire a useful quantum entanglement as well. This is especially expected in a covalent bond formed between an electronegative atom and a H atom. Also, if such a covalent bond participates in a classical H-bond by electrostatically interacting with another electronegative atom, it gains much more ionic character and so the amount of useful entanglement is enhanced. Conversely, we demonstrated that tunneling of either the electrons of the proton-acceptor atom or the proton of the H atom can generate useful quantum entanglement in a H-bonded system, and the amount of this entanglement increases with a decrease in the amount of ionic character of the proton-donating covalent bond. Also, a significant amount of entanglement can be shared between the atoms in such a partially covalent H-bond even in the thermal equilibrium.

Could it be possible for biological organisms to utilize the useful entanglement shared in partially covalent H-bonds? To explore this question, we constructed a hypothetical molecular recognition scenario in which a receptor protein or an enzyme recognizes its ligands using $n$ intermolecular H-bonds involving proton or electron delocalization. We restricted the biomolecule under consideration to participate in each of these H-bonds with the same set of proton-acceptors and donors residing on its binding site. We found that $3^n - 1$ agonist ligands can be discriminated by the biomolecule when the intermolecular entanglements are teleported into its intramolecular H-bonds by means of the effect of its conformation on both its intra- and intermolecular H-bonds.

Discrimination of $3^n - 1$ ligands under such a restricted circumstance corresponds to an enormously high efficiency of the usage of H-bonds as resource in molecular recognition. To reveal this more precisely, we summarized the molecular recognition processes involved in DNA replication and protein synthesis. Although these processes are quite accurate and very fast, our spurious biomolecule was found to be superior than the polymerase and synthetase enzymes in the sense that it singles out more ligands using less H-bond acceptors and donors in ligand recognition. Finally, we considered the primordial ancestors of the contemporary synthetases that may have lived in pre-DNA world. As these ancient enzymes were probably discriminating more ligands using less H-bonds, we argued that quantum entanglement shared in synthetase-ligand H-bonds may have been somehow used as resource in molecular recognition until the emergence of more complex enzymes in the evolution of genetic machinery.
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Appendix: Entanglement swapping protocol

In what follows, we will construct a simple protocol for the two-step state transformation given as

$$|\phi\rangle = (|\alpha\rangle_{10} + |\beta\rangle_{00} + |\gamma\rangle_{01})_{X_N X_1} \otimes \left(\frac{|1\rangle - |0\rangle}{\sqrt{2}}\right)_{X_2}$$

Measurement on $X_N$ in the basis of $\{|\lambda_1\rangle = \lambda_1|1\rangle + \lambda_2|0\rangle, |\lambda_2\rangle = |1\rangle - |0\rangle\}$

Local operations on joint $X_1 X_2$ system depending on the measurement outcome

$$(|\alpha\rangle_{10} + |\beta\rangle_{00} + |\gamma\rangle_{01})_{X_2 X_1} \otimes |\psi\rangle_{X_N} \equiv |\psi\rangle,$$

where $|\alpha|^2 + |\beta|^2 + |\gamma|^2 = 1$, $|\lambda_1|^2 + |\lambda_2|^2 = 1$, $N = \{|B, C\}$, $|\psi\rangle_{X_N} = \lambda_1|1\rangle + \lambda_2|0\rangle$, and $|\psi\rangle_{X_N} = |\lambda^*_1|1\rangle - |\lambda^*_2|0\rangle$.

Assume without any loss of generality that $\beta = 0$ and $\lambda_1 = \lambda_2 = 1/\sqrt{2}$. The former assumption maximizes the entanglement shared in the initial intermolecular H-bond by minimizing the ionic character of the proton donating $X_N$–H covalent bond during the interaction with proton-acceptor $X_1$. On the other hand, the latter assumption attributes the same amount of ionic character to both $X_B$–H and $X_C$–H covalent bonds in the absence of any interaction with $X_1$.

Note that the computational basis states can be written as

$$|0\rangle = \frac{|+\rangle + |\rangle}{\sqrt{2}}, \quad |1\rangle = \frac{|+\rangle - |\rangle}{\sqrt{2}},$$

where $|\rangle = \frac{1}{\sqrt{2}}(|0\rangle \pm |1\rangle)$. Before making a measurement on $X_N$ in the basis of $\{|\pm\rangle\}$, let us rewrite the initial state in this basis as

$$|\phi\rangle = \frac{1}{\sqrt{2}}(|\alpha\rangle_{10} - |\alpha\rangle_{100} + |\gamma\rangle_{011} - |\gamma\rangle_{0101})_{X_N X_1 X_2}$$

$$= \frac{1}{\sqrt{2}} \left( |\alpha\rangle_{10} + |\alpha\rangle_{001} + |\gamma\rangle_{011} - |\gamma\rangle_{0101} \right)_{X_N X_1 X_2}$$

where

$$|\alpha\rangle = \frac{1}{\sqrt{2}} \left( |\alpha\rangle_{010} + |\alpha\rangle_{001} + |\gamma\rangle_{011} - |\gamma\rangle_{0101} \right)_{X_N X_1 X_2}.$$
if $|\psi\rangle_{X_N}$ is found to be $|+\rangle$ by the measurement, while it equals to

$$
|\psi\rangle_{X_1X_2} = \frac{1}{\sqrt{2}} \left( \alpha_+ |01\rangle - \alpha_+ |00\rangle - \gamma_+ |11\rangle + \gamma_+ |10\rangle \right)_{X_1X_2},
$$

(A.5)

otherwise.

The second step of the protocol given in (A.1) starts with a conditional operation applied only on $X_2$ depending on the measurement outcome: if $|\psi\rangle_{X_N}$ is measured as $|-\rangle$, $X_2$ is subjected to a Pauli $Z$ operation, a unitary transformation that equals to $|0\rangle \langle 0| - |1\rangle \langle 1|$. The conditional operation defined in this way brings the state of $X_1X_2$ joint system into (A.4) in either case, and is followed by a joint unitary operation on $X_1X_2$ which implies the state transformations to be

$$
\frac{1}{\sqrt{2}} (|01\rangle - |00\rangle)_{X_1X_2} \rightarrow |01\rangle_{X_1X_2}, \quad \frac{1}{\sqrt{2}} (|11\rangle + |10\rangle)_{X_1X_2} \rightarrow |11\rangle_{X_1X_2},
$$

$$
\frac{1}{\sqrt{2}} (|11\rangle - |10\rangle)_{X_1X_2} \rightarrow |10\rangle_{X_1X_2}, \quad \frac{1}{\sqrt{2}} (|01\rangle + |00\rangle)_{X_1X_2} \rightarrow |00\rangle_{X_1X_2}.
$$

(A.6)

After these two subsequent operations, the $X_1X_2$ joint system ends up in the target state given by

$$
|\psi\rangle_{X_1X_2} = (\alpha_+ |01\rangle + \gamma_+ |10\rangle)_{X_1X_2}.
$$

(A.7)

As Pauli $Z$ operation implies the state transformations $|-\rangle \leftrightarrow |+\rangle$, its application on $X_2$ in the beginning of the second step of the protocol physically corresponds to a switch between two distinguishable states of $X_2$—H covalent bond each of which possesses 50 percent ionic character. Besides this, the two state transformations given in the first line of (A.6) physically correspond to disappearance of the ionic character of $X_2$—H covalent bond. Conversely, the two state transformations given in the next line describe a process in which $X_2$—H covalent bond breaks down and becomes a completely ionic bond. Note that none of the input states of the joint unitary operation defined in (A.6) is entangled, but $X_2$—H covalent bond possesses 50 percent ionic character in each of them. Also note that the initial state of $X_2$ in (A.1) is ionic to the same extent. Hence, all the quantum operations involved in the present entanglement swapping protocol, expect the initial measurement on $X_N$, are somehow related to the amount of ionic character of the $X_2$—H covalent bond, which may take the values of 0, 50, or 100 percent. We propose that, likewise the measurements discussed in Section V, these operations can be also regarded as an influence of the conformational dynamics on the $X_2$—H covalent bond.