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A quantum mechanical model of adaptive mutation

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Abstract

The principle that mutations occur randomly with respect to the direction of evolutionary change has been challenged by the phenomenon of adaptive mutations. There is currently no entirely satisfactory theory to account for how a cell can selectively mutate certain genes in response to environmental signals. However, spontaneous mutations are initiated by quantum events such as the shift of a single proton (hydrogen atom) from one site to an adjacent one. We consider here the wave function describing the quantum state of the genome as being in a coherent linear superposition of states describing both the shifted and unshifted protons. Quantum coherence will be destroyed by the process of *decoherence* in which the quantum state of the genome becomes correlated (entangled) with its surroundings. Using a very simple model we estimate the decoherence times for protons within DNA and demonstrate that quantum coherence may be maintained for biological time-scales. Interaction of the coherent genome wave function with environments containing utilisable substrate will induce rapid decoherence and thereby destroy the superposition of mutant and non-mutant states. We show that this accelerated rate of decoherence may significantly increase the rate of production of the mutated state.

Keywords: Adaptive mutations; Quantum coherence; Wave function

1. Introduction

Neo-Darwinian evolutionary theory is founded on the principle that mutations occur randomly, and the direction of evolutionary change is provided by selection for advantageous mutations. However the central tenet, that mutations occur randomly, has recently been challenged by the finding of the phenomenon termed adaptive or directed mutation. This type of mutation was initially detected when a non-fermenting strain of *Escherichia coli* was plated onto rich media containing lactose. In experiments described by Cairns et al. (1988), papillae of *lac*$^+$ lactose-fermenting mutants arose over a period of several weeks yet mutations that did not confer any selec-

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tive advantage did not appear during the incubation. In parallel experiments *lac*$^+$ mutants arose at much lower frequencies in the absence of lactose. Adaptive mutations have since been reported in other bacteria and eukaryotes, as reported by Hall (1990, 1991, 1995, 1997, 1998), Foster and Cairns (1992), Wilke and Adams (1992), Steele and Jinks Robertson (1992), Rosenberg et al. (1994). Although some of the earlier observations have been called into question by more recent experiments by Foster (1997) and Prival and Cebula (1996), they remain a very controversial and hotly debated phenomenon. Adaptive mutations differ from standard mutations in that (i) they only occur in cells that are not dividing or dividing only rarely, (ii) they are time-dependent not replication-dependent, (iii) they appear only after the cell is exposed to the selective pressure. There is, therefore, no entirely satisfactory theory to account for how a cell can selectively mutate certain genes in response to environmental signals. Hall (1997) has commented in a recent paper that '. . . the selective generation of mutations by unknown means is a class of models that cannot and should not, be rejected'.

As initially proposed by Delbruck et al. (1935) and Schrödinger (1944) and Watson and Crick (1953), spontaneous mutations are initiated by quantum jump events such as tautomeric shifts in single protons of DNA bases. Lowdin (1965), Topal and Fresco, (1976), Matsuno, (1992, 1995), Cooper (1994), Florian and Leszczynski (1996) and Rosen (1996) have proposed that the living cell may act as a quantum measurement device that monitors the state of its own DNA. Home and Chattopadhyaya (1996) suggested that DNA may persist as a superposition of mutational states in a biomolecular version of Schrödinger's cat paradox. Goswami and Todd (1997) and Ogryzko (1997) have recently proposed that adaptive mutations may be generated by environment-induced collapse of the quantum wave function describing DNA in a superposition of mutational states. For such a mechanisms to be feasible, the evolving DNA wave function must remain coherent for long enough for it to interact with the cell's environment. We here investigate this possibility by modelling a specific mutational process involving quantum tunnelling and estimate the rate of decoherence for the coding protons initiating mutational events within DNA. We demonstrate that DNA coding information may remain coherent for biologically feasible periods of time. We show that the strength of coupling between the DNA wave function and its environment has the potential to accelerate the rate of decoherence and thereby enhance mutation rates to cause adaptive mutations.

2. Model and results

2.1. Initiation of mutations

For ease of analysis, we will consider a population of c cells each with a genome containing two genes A and B which, under non-adaptive conditions in the stationary phase, mutate to mutant alleles a and b at approximately the same rate, P, per unit time interval per gene. Lowdin (1965) pointed out that genetic information is encoded by a linear array of protons and proposed a model for generation of mutations involving base tautomers, in which a base substitution is caused by (1) generation of a tautomeric form of a DNA base in the non-coding strand of a gene by a single proton shift between two adjacent sites within the base (e.g. keto guanine → enol guanine), (2) incorporation of an incorrect base into the coding strand due to anomalous base-pairing of the tautomeric form (e.g. enol guanine:keto thymine), during repair-directed DNA synthesis in non-growing cells to cause a transition mutation C → T. Subsequent transcription and translation of the mutant form of the gene will result in expression of the mutant phenotype.

The Lowdin two-step model for generation of a mutations is initiated by a quantum tunnelling process of an H-bonded proton between two adjacent sites within base pairs (Lowdin, 1965). Thus, at any given time the state of the proton must be described as a wave function which is a linear superposition of position states in which the proton has either tunnelled or not tunnelled.

$$|\Phi_{\text{proton}}\rangle = \alpha|\Phi_{\text{not tun.}}\rangle + \beta|\Phi_{\text{tun.}}\rangle \quad (1)$$

where α and β are complex numbers describing the amplitude of the *not tunnelled* and *tunnelled* states, respectively.

During DNA replication, the wave function will evolve to incorporate both the correct base (C for $|\Phi_{\text{not tun.}}\rangle$) and the incorrect base (T for $|\Phi_{\text{tun.}}\rangle$) as a linear superposition of the unmutated and mutated states of the daughter DNA strand. The daughter DNA strand will be described by a wave-function $|\Psi_{\text{G}}\rangle$ that consists of a superposition of the unmutated and mutated states:

$$|\Psi_{\text{G}}\rangle = \alpha|\Phi_{\text{not tun.}}\rangle|\text{C}\rangle + \beta|\Phi_{\text{tun.}}\rangle|\text{T}\rangle \quad (2)$$

The wave function will continue to evolve as the coding strand (containing either C or T at locus) is transcribed and translated resulting in a wild-type and mutant form of the protein, say *lacZ* containing an arginine→histidine amino acid substitution that results in a $lac^- \rightarrow lac^+$ mutation in cells plated onto media without lactose) such that the cell may be described as a linear superposition of the unmutated and mutated states:

$$|\Psi_{\text{cell}}\rangle = \alpha|\Phi_{\text{not tun.}}\rangle|\text{C}\rangle|\text{Arg}\rangle + \beta|\Phi_{\text{tun.}}\rangle|\text{T}\rangle|\text{His}\rangle \quad (3)$$

The time taken for the cell to reach this state after the initial mutational event (proton tunnelling) can be estimated. The mutational process involving DNA repair is likely to be relatively rapid (DNA polymerase incorporates nucleotides at a rate of about 500–1000 nucleotides per second). Emergence of the mutant phenotype via coupled transcription/translation will be limited by the slower rate of translation, estimated as about 20 amino acid residues per second for *E. coli* ribosomes, as described by Alberts et al. (1994). We estimate that *E. coli* would reach the mutant state in a time somewhere between 1 and 100 s (depending on the size of protein) after the tunnelling event. A key part of our proposal is that this is a feasible period of time for superpositions of quantum states to be maintained within a living cell. We will next examine this proposition.

3. Decoherence

The role of the interaction between a quantum system and its environment, and the transition from quantum to classical reality, has been a subject of increasing interest in physics over the last few years. The emergence of classical behaviour from quantum dynamics can be traced back to the measurement problem in quantum mechanics as analysed by the mathematician Von Neumann (1932). In its simplest form, a measurement is carried out on a quantum system in a superposition of two states. Initially, the system is in a pure state, but its surroundings (the environment) act as a quantum detector that interacts with the system. This coupling between system and detector results in a correlated (or entangled) state in which the superposed system becomes entangled with its surroundings that must then also exist as a superposition. Formally, this correlation between the possible states of the system and those of the environment is expressed in terms of a density matrix that contains information about the alternative outcomes of the measurement. In particular, it will contain off diagonal terms that are responsible for the non-classical behaviour (interference effects). Von Neumann postulated that the process of 'measurement' occurs via an ad hoc 'reduction of the state vector' in which the density matrix is reduced to one that no longer contains the off diagonal terms but only those diagonal terms that correspond to possible classical outcomes (e.g. Schrödinger's cat which is either dead or alive but not in a state that is in a superposition of both dead and alive). The standard (Copenhagen) interpretation of quantum mechanics considers that a quantum state will remain as a superposition until a measurement is made by a conscious observer, forcing the system to choose a single classical state and thereby 'collapse' the wave function. This interpretation would therefore have no problem with the concept of quantum superpositions of complex biological systems; the entire bacterial cell could exist as a microbial variant of the famous 'Schrödinger cat' superposition. More recently, Zurek (1991) and others have suggested that wave-function collapse is determined entirely by the dynamics of

the quantum system and its interaction with the environment. These models predict that coherent superpositions of quantum states will decohere into a statistical ensemble of macroscopically distinguishable (classical) states whenever the system reaches a critical degree of complexity or interacts with a complex environment. Essentially, the numerous interactions between the system and its environment cancel out all of the interference terms (that lead to non-classical behaviour) in the Schrödinger equation governing the dynamics of the system. The environment here means anything that can be affected by the quantum system and hence gain information about its state. The environment is hence constantly monitoring the system. The claim being made in this paper is that living cells can themselves form unique quantum measuring devices that probe individual quantum processes going on in their interior.

The difficulty with trying to compute the decoherence time scale is that we need to define a suitable measure of the effectiveness of the process of decoherence. One of the most popular models is to take the quantum system to be a single particle moving in one dimension while the environment is a 'heat bath' modelled as a set of harmonic oscillators. In such a model, the effect of the environment is related to the number density of oscillators with a given frequency and to the strength of the coupling between these oscillators and the system. Within this simple model, Zurek (1991) has derived an expression for the decoherence time scale over which quantum coherence is lost. If a system of mass m is in a superposition of two position states (modelled as two Gaussian wave packets) separated spatially by a distance Δx then the decoherence time, t_D, is defined to be:

$$t_D = t_R\left(\frac{\lambda_T}{\Delta x}\right)^2 \tag{4}$$

where $\lambda_T = \hbar\sqrt{2mk_BT}$, is the thermal de Broglie wavelength that depends only the temperature T of the surrounding environment and for a proton at 300 K works out as 0.27 Å. The relaxation time t_R, is the time taken for the wave packets to dissipate the energy difference between the coherent states. The separation of protons, Δx, between enol and amine states for a DNA base is about 0.5 Å. Therefore,

$$t_D = 0.29t_R \tag{5}$$

Quantum coherence would be expected to persist for approximately one quarter of the relaxation time. The relaxation time is a measure of the speed of energy dissipation due to interaction of the proton with particles in its immediate environment. This is unknown for coding protons in DNA within living cells. However, some measure of the possible range of energy dissipation times for protons in living systems may be gained from examination of proton relaxation rates in biological materials, as measured by nuclear magnetic resonance (NMR). In NMR, a pulse of electromagnetic radiation is used to perturb the magnetic dipole moment of nuclei aligned in a magnetic field. The pulse causes the nuclei to process coherently about the direction of the applied electromagnetic field. After the pulse of the field, the protons return to their ground state by exchanging energy with the atoms and molecules in their environment. The NMR spin–latice relaxation time T_1, gives a measure of the rate of this energy loss to the environment. Agback et al. (1994) measured NMR proton relaxation rates (T_1) in DNA oligomers in solution and obtained values ranging from milliseconds to seconds. NMR T_1 values have also been measured for living cells and tissue as reported by Beall et al. (1984) and range from milliseconds to many seconds. *E. coli* cells have a T_1 relaxation time of 557 ms. Although the exact relationship between the NMR T_1 value and the relaxation rate t_R of Eq. (4) is far from clear, they are both a measure of the rate of energy exchange between a proton and its environment. In fact, it should be remembered that NMR-based proton relaxation rates relate to the bulk of protons in living tissue that are mostly associated with water. Proton relaxation times for protons within much more constrained structures such as DNA are likely to be much longer but are currently unknown. Also, for protons existing as a superposition of DNA base tautomeric position states, an energy barrier exists between the two states, which stabilise the energy difference against dissipation. We therefore conclude that

relaxation times for coding protons within a DNA double helix are likely to be of the order of seconds which, from Eq. (5), implies that quantum coherence may be maintained for a sufficient lengthy period of time (1–100 s or longer) to allow the cell to evolve into a superposition of mutated and non mutated states.

4. Accelerated decoherence by the environment for mutant states

If the linear superposition of the cell is maintained, then the cell's wave-function $|\Psi_{\text{cell}}\rangle$ will eventually couple with the lactose present in the environment. It is at this stage that there is a crucial difference between the same mutation under adaptive and non-adaptive conditions (Fig. 1).

In conditions in which the mutation is not adaptive (e.g. when the cells are plated on media without lactose), then the two components of the above wave equation (mutant and non-mutant states) are indistinguishable by the cell. DNA, RNA and protein will differ only at single residues and, therefore, only involve relatively small-scale atomic displacements for very small numbers of particles. We propose that under these conditions, quantum coherence persists within the cell for a relatively long period of time, t_{D1}, before decoherence intervenes to precipitate the emergence of classical mutant and non-mutant states (Fig. 1(a)). Mutants will therefore accumulate with time, at a rate proportional to $1/t_{\text{D1}}$.

However, if the mutation is adaptive (e.g. $lac^- \rightarrow lac^+$ in cells plated onto lactose media), then the mutant cell will be able to utilise lactose to provide energy for growth and replication. The cell's wave function $|\Psi_{\text{cell}}\rangle$ will couple with the lactose.

$$|\Psi_{\text{cell}}\rangle = \alpha|\Phi_{\text{not tun.}}\rangle|\text{C}\rangle|\text{Arg}\rangle|\text{lactose}\rangle + \beta|\Phi_{\text{tun.}}\rangle|\text{T}\rangle|\text{His}\rangle|\text{lactose}\rangle \quad (6)$$

Since a single enzyme molecule can hydrolyse many thousands of substrate molecules, then the mutation will rapidly cause changes in position for many millions of particles within the cell. The superposition of proton position states can no longer be considered in isolation but must include position shifts for many millions of particles within the cell. This will cause almost instantaneous decoherence, as can be seen by reference to Eq. (4). If, instead of a single proton of mass 1.6×10^{-27} kg, the superposition is estimated to include just 10^6 protons (a very conservative estimate of the number of shifted particles in conditions wherein lactose is hydrolysed) with a total mass of 1.6×10^{-21} kg, then the de Broglie wavelength ($\lambda_{\text{T}} = \hbar\sqrt{2mk_{\text{B}}T}$) reduces to 0.0018 Å. If each particle experiences a position shift of 0.5 Å, then decoherence time, t_{D2}, is reduced to $1.3 \times 10^{-5} t_{\text{R}}$. When a superposition of states involves a large mass then the environment causes rapid decoherence of the states. Once the mutation couples with the environment then the superposition of alternative states described by Eq. (6) will decohere into the familiar classical states of mutant and non-mutant cells after the relatively short period of time, t_{D2}:

$$\alpha|\Phi_{\text{not tun.}}\rangle|\text{C}\rangle|\text{Arg}\rangle|\text{lactose}\rangle + \beta|\Phi_{\text{tun.}}\rangle|\text{T}\rangle|\text{His}\rangle|\text{lactose}\rangle \rightarrow |\Phi_{\text{not tun.}}\rangle|\text{C}\rangle|\text{Arg}\rangle|\text{lactose}\rangle \quad or \quad |\Phi_{\text{tun.}}\rangle|\text{T}\rangle|\text{His}\rangle|\text{lactose}\rangle \quad (7)$$

Cells that collapse into the non-mutant state will be however remain at the quantum level. Their coding protons will again be free to tunnel into the tautomeric position and evolve to reach the superposition of mutant and non-mutant states, as described by Eq. (1). However, any cell that decoheres into the mutant state will grow and replicate into a bacterial colony. Environment-induced decoherence will precipitate the emergence of mutant states, but at a rate t_{D2} which will be much less than t_{D1}, the time for decoherence in the absence of lactose. Under adaptive conditions, the mutant state (and of course only mutants that can grow on lactose—adaptive mutations—*will* grow) will precipitate out of the quantum superposition at a high rate, relative to their rate of generation in non-adaptive conditions. The increased rate, due to enhanced environmental coupling, will be proportional to the ratio of the two decoherence times: $t_{\text{D1}}/t_{\text{D2}}$. Mutations will occur

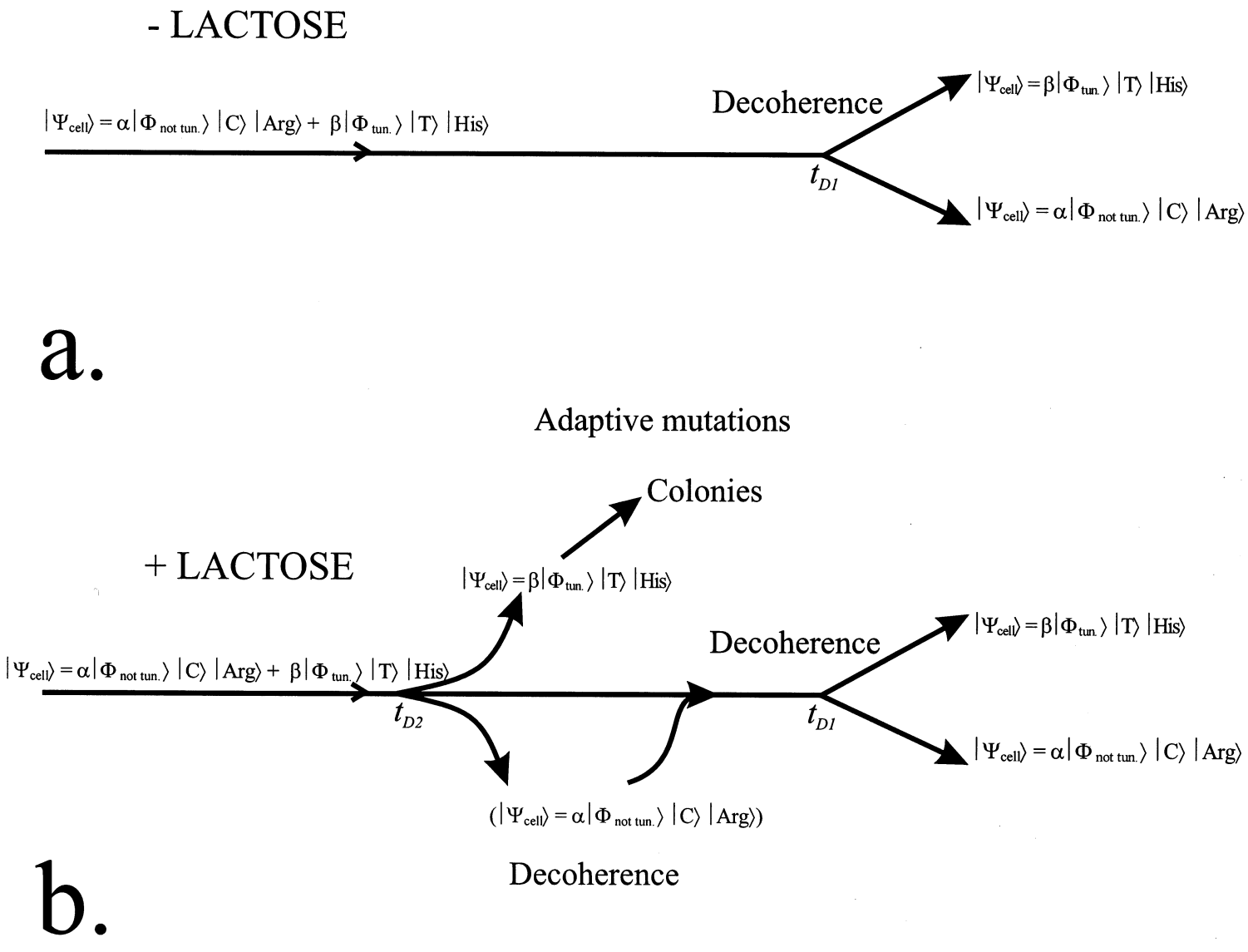

Fig. 1. Dynamics of the wave function of a bacterium undergoing a mutational change, C→T, giving rise to an arginine→histidine amino acid shift. The presence of histidine is considered adaptive in environments containing lactose. (a) No lactose present; (b) in environments containing lactose.

more frequently under conditions where they allow the cell to grow—adaptive mutations.

5. Dicussion

All biological phenomena involve the movement of fundamental particles such as protons or electrons within living cells and as such, are properly described by quantum rather than classical mechanics. Physicists have long been aware of this fact but its implications have not been fully explored in biology. Frolich, (1970), Frolich (1975) and Penrose (1995) have proposed that quantum phenomena occur in biological systems. Both proton and electron tunnelling are thought to be involved in enzyme action and mutation (Topal and Fresco, 1976; Cooper, 1994) and electron tunnelling is thought to be involved in electron transport in respiration and photosynthesis. Gider et al. (1995) claimed to detect quantum coherence effects within the ferritin protein. Schrödinger (1944) proposed that 'The living organism seems to be a macroscopic system which in part of its behaviour approaches purely mechanical (as contrasted to thermodynamical) behaviour to which all systems tend as the temperature approaches the absolute zero and the molecular disorder is removed'. By reference to temperatures near absolute zero (at which all dynamics become quantum mechanical), Schrödinger implies that the behaviour of living organisms approaches quantum mechanical behaviour. More recently, Home and Chattopadhyaya (1996) suggested that DNA may persist as a superposition of mutational states in a biomolecular version of Schrödinger's cat paradox. The components of living cells may therefore maintain an ordered structure that is compatible with retention of quantum coherence at much higher temperatures than those that would be expected to destroy the quantum state of inanimate systems.

Living organisms are not of course unique in being composed of fundamental particles. What is unique is that the coupling between fundamental particles and the environment of living cells enables their macroscopic behaviour to be determined by quantum rather than classical laws. As Schrödinger pointed out in his 1944 essay, statistical laws such as thermodynamics dominate all other natural phenomena. For instance, the motion of particles that govern the action of heat engines, chemical engines or electrical engines is, at the level of individual particles, entirely random and incoherent. Slight statistical deviations from randomness cause the macroscopic behaviour associated with these devices. In modern terminology, decoherence wipes out the quantum phenomena going on at the microscopic level. In contrast, the macroscopic behaviour of living cells may be determined by the dynamics of individual particles and thereby be subject to quantum, rather than statistical laws. An example of such a coupling between the macroscopic properties of cells and individual particles is, as we describe here, the entanglement that develops between the dynamics of single particles within the DNA molecule and mutations.

In our model, the motion of individual protons within DNA bases becomes entangled with the environment. In essence, the environment performs a quantum measurement of the position of the target proton. It is a well-established fact that quantum measurement has the ability to influence the dynamics of a quantum system. Indeed, Heisenberg's uncertainty principle guarantees that a quantum measurement will always influence the dynamics of a quantum system. The quantum Zeno effect and the inverse quantum Zeno effect are particularly striking examples of how measurement can influence the dynamics of quantum systems. In the quantum Zeno effect, continuous measurement of a quantum system freezes the dynamics of that system as described by Itano et al. (1990) and Altenmuller and Schenzle (1994). In the inverse quantum Zeno effect, a dense series of measurements of a particle along a chosen path, can force the dynamics of that particle to evolve along that path, as described by Aharonov and Vardi (1980) and Altenmuller and Schenzle (1993).

In this study we choose to model a mutational event that is initiated by a tautomeric proton shift subject to quantum tunnelling effects, since this model is mechanistically amenable to quantum mechanical treatment. Naturally occurring muta-

tions may be caused by a variety of mechanisms including radiation-induced ionisation, UV-induced pyrimidine dimer formation, chemical modification by mutagens, and tautomer-induced mis-pairing during DNA replication. Yet, all these mutational mechanisms are initiated by chemical modifications to the genetic code and must therefore involve the adsorption and/or displacement of fundamental particles (photons, electrons, protons) within the DNA strand and be subject to quantum mechanical effects.

The potential of quantum mechanics to influence the macroscopic phenomenon of mutation will depend on the ability of the system to remain as a coherent quantum state throughout the mutational process. Our estimates for decoherence times for coding protons in DNA are based on currently available information and are necessarily preliminary but do demonstrate that quantum mechanical dynamics might persist for biologically feasible periods of time. Further data in this area, particularly the use of physical techniques such as NMR to attempt to detect quantum effects in live tissue, are urgently needed.

We demonstrate in this paper that the dynamics of particles that cause mutations may be entangled with the environment of the living cell. The complexity of that entanglement will be dependent upon the composition of the environment. In some circumstances (in our model, absence of lactose) there will be only minimal entanglement and the quantum superposition may remain coherent for lengthy periods of time. Under these circumstances, the environment will not measure the position state of the target particle and it will persists as a quantum superposition. However, when lactose is added to the environment then the state of the proton becomes entangled with a much more complex environment that causes rapid decoherence. In effect, the environment performs a dense series of measurements of the position state of the target proton. As we discussed above, quantum measurement will always influence the dynamics of any quantum system being measured. We demonstrate in our model that accelerated decoherence caused by the presence of lactose, has the potential to accelerate the generation of the mutant state out of the quantum superposition. This is precisely the phenomenon of adaptive mutations. The phenomenon bears many similarities to the inverse quantum Zeno effect, as described by Aharonov and Vardi (1980) and Altenmuller and Schenzle (1993), whereby a dense series of measurements along a particular path will force a quantum system to evolve along that path.

In this paper we use a plausible physical model to show that the coupling of the quantum state representing the mutational event, with the environment of the cell can enhance the probability of that mutation. The model is compatible with current physical theory and requires no new mutational mechanisms. It projects natural selection as acting within the framework of the evolving genome wave function consisting of a superposition of all possible mutational states available to the cell. Coupling between the wave function and the environment allows the cell to simultaneously sample the vast mutational spectra as a quantum superposition. An analogous situation is the concept of quantum computing whereby the wave function of a computer can exists as a quantum superposition of many computations carried out simultaneously, as described by DiVincenzo (1995). Living cells could similarly act as biological quantum computers, able to simultaneously explore multiple possible mutational states and collapse towards those states that provide the greatest advantage.

References

Agback, P., Maltseva, T.V., Yamakage, S.I., Nilson, F.P., Foldesi, A., Chattopadhyaya, J., 1994. The differences in the T2 relaxation rates of the protons in the partially-deuteriated and fully protonated sugar residues in a large oligo-DNA ('NMR-window') gives complementary structural information. Nucleic Acids Res. 22, 1404–1412.

Aharonov, Y., Vardi, M., 1980. Meaning of an individual 'Feynman path'. Phys. Rev. D 21, 2235–2240.

Alberts, B., Bray, D., Lewis, J., Roberts, K., Watson, J.D., 1994. Molecular Biology of the Cell. Garland Publishing, New York.

Altenmuller, T.P., Schenzle, A., 1993. Dynamics by measurement: Aharonov's inverse quantum Zeno effect. Phys. Rev. A 48, 70–79.

Altenmuller, T.P., Schenzle, A., 1994. Quantum Zeno effect in a double-well potential-a model of a physical measurement. Phys. Rev. A 49, 2016–2027.

Beall, P.T., Amtey, S.R., Kasturi, S.R., 1984. NMR Data Handbook for Biomedical Applications. Pergamon Press, Oxford.

Cairns, J., Overbaugh, J., Millar, S., 1988. The origin of mutants. Nature 335, 142–145.

Cooper, W.G., 1994. T4-phage evolution data in terms of a time-dependent Topal–Fresco mechanism. Biochem. Genet. 32, 383–395.

Delbruck, M., Timofeeff, N.W., Zimmer, K.G., 1935. Nachr. Biol. Ges. Wiss. Gottingen 1, 189.

DiVincenzo, D.P., 1995. Quantum computation. Science 270, 255–261.

Florian, J., Leszczynski, J., 1996. Spontaneous DNA mutations induced by proton transfer in the guanine cytosine base pairs: an energetic perspective. J. Am. Chem. Soc. 118, 3010–3017.

Foster, P.L., 1997. Nonadaptive mutations occur on the F′ episome during adaptive mutation conditions in *Escherichia coli*. J. Bacteriol. 179, 1550–1554.

Foster, P.L., Cairns, J., 1992. Mechanisms of directed mutation. Genetics 131, 783–789.

Frolich, H., 1970. Long range coherence and the actions of enzymes. Nature 228, 1093.

Frolich, H., 1975. The extraordinary dielectric properties of biological materials and the action of enzymes. Proc. Natl. Acad. Sci. USA 72, 4211–4215.

Gider, S., Awschalom, D.D., Douglas, T., Mann, S., Chaparala, M., 1995. Classical and quantum magnetic phenonena in natural and artificial ferritin proteins. Science 268, 77–80.

Goswami, A., Todd, D., 1997. Is there conscious choice in directed mutation, phenocopies, and related phenomena? An answer based on quantum measurement theory. Integr. Physiol. Behav. Sci. 32, 132–142.

Hall, B.G., 1990. Spontaneous point mutations that occur more often when advantageous than when neutral. Genetics 126, 5–16.

Hall, B.G., 1991. Adaptive evolution that requires multiple spontaneous mutations: mutations involving base substitutions. Proc. Natl. Acad. Sci. USA 88, 5882–5886.

Hall, B.G., 1995. Adaptive mutations in Escherichia coli as a model for the multiple mutational origins of tumors. Proc. Natl. Acad. Sci. USA 92, 5669–5673.

Hall, B.G., 1997. Spontaneous point mutations that occur more often when advantageous than when neutral. Genetics 126, 5–16.

Hall, B.G., 1998. Adaptive mutagenesis at ebgR is regulated by PhoPQ. J. Bacteriol. 180, 2862–2865.

Home, D., Chattopadhyaya, R., 1996. DNA molecular cousin of Schrodinger's cat: a curious example of quantum measurement. Phys. Rev. Letts. 76, 2836–2839.

Itano, W.M., Heinzen, D.J., Bollinger, J.J., Wineland, D.J., 1990. Quantum Zeno effect. Phys. Rev. A 41, 2295–2300.

Lowdin, P.O., 1965. Quantum genetics and the aperiodic solid. Some aspects on the Biological problems of heredity, mutations, aging and tumours in view of the quantum theory of the DNA molecule. In: Lowdin, P.O. (Ed.), Advances in Quantum Chemistry, vol. 2. Academic Press, New York, pp. 213–360.

Matsuno, K., 1992. The uncertainty principle as an evolutionary engine. Biosystems 27, 63–76.

Matsuno, K., 1995. Quantum and biological computation. Biosystems 35, 209–212.

Ogryzko, V.V., 1997. A quantum-theorertical approach to the phenomenon of directed mutations in bacteria (hypothesis). Biosystems 43, 83–95.

Penrose, R., 1995. Shadows of the Mind. Oxford University Press, London.

Prival, M.J., Cebula, T.A., 1996. Adaptive mutation and slow-growing revertants of an *Escherichia coli* lacZ amber mutant. Genetics 144, 1337–1341.

Rosen, R., 1996. Biology and the measurement problem. Comput. Chem. 20, 95–100.

Rosenberg, S.M., Longerich, S., Gee, P., Harris, R.S., 1994. Adaptive mutation by deletions in small mononucleotide repeats [see comments]. Science 265, 405–407.

Schrödinger, E., 1944. What is Life? Cambridge University Press, London.

Steele, D.F., Jinks Robertson, S., 1992. An examination of adaptive reversion in *Saccharomyces cerevisiae*. Genetics 132, 9–21.

Topal, M.D., Fresco, J.R., 1976. Complementary base pairing and the origin of substitution mutations. Nature 263, 285–289.

Von Neumann, J. (1932). Mathematical Foundations of Quantum Mechanics (English translation R. T. Beyer), Princeton University Press.

Watson, J.D., Crick, F.H.C., 1953. Genetic implications of the structure of deoxyribonucleic acid. Nature 171, 964–969.

Wilke, C.M., Adams, J., 1992. Fitness effects of Ty transposition in *Saccharomyces cerevisiae*. Genetics 131, 31–42.

Zurek, W.H., 1991. Decoherence and the transition from quantum to classical. Phys. Today October 1991, 36–44.