Reliability of Nano Devices and Systems: Nuclear Spins of Stable Magnetic Isotopes as the Reliability Factors of Biomolecular Nanoreactors

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ABSTRACT

The trend of nanoscaling brings engineering down to the dimensions of molecular structures. However, it also poses the problem of how to create a reliable system from molecular components which experience permanent thermal and environmental fluctuations. Reliability ("robustness") is defined as the ability of a device to perform its function for a given time under given conditions. Fortunately, engineers may learn wisdom by the examples of Nature ("bionics"), to achieve the high systems reliability while dealing with unreliable components. There are several lines of creating reliable devices from unreliable functional elements in nanoengineering, the main of which is a preventive maintenance of components and prophylaxis of failures. The goal of this paper is to demonstrate how magnesium-25 and other kinds of stable magnetic isotopes are promising, on the spin-chemistry basis, for optoelectronics and nanophotonics to improve efficiency and reliability of the relevant molecular devices.

***Key words*:** nanotechnology, nanoengineering, reliability, nanoreactors, isotopes

1 THE PROBLEM OF RELIABILITY

Nanotechnology – a catchall term for engineering materials sized between 1 and 100 billionths of a meter – is widely seen as having enormous scientific and commercial potential. The idea that engineering can be extended towards the molecular scale, to electronic devices of high efficiency based on single molecules and so on, has become currency over the past decade. This trend of nanoscaling brings engineering down to the dimensions of molecular structures. At the same time, it brings technical devices down to nanoengineering and, as a consequence, intrinsic instability of functional parameters due to thermal, mechanic and other fluctuations. This aggravates the problem of reliability in nanoengineering (see, for examples, references [1] and [2]).

Reliability ("robustness") is defined as the ability of a device to perform its function for a given time under given conditions [3]. In mathematical theory of reliability, a time-dependent m-dimensional vector $\boldsymbol{Y(t)}$ is brought into use, each k-element of which ($k = 1, 2, \ldots, m$) corresponds to the relevant functional parameter of the device, and the relevant admissible limits of the parameters are introduced. If values of Y_k are in the limits, then the state of the device is defined as normal operation during the given time. If any of Y_k occurs beyond the limits, then we say that the device is in the state of failure. Inasmuch as the device performs its functions in the presence of random factors all Y_k are random values. Moreover, the admissible limits of the functional parameters may also be time-dependent and stochastic. Accordingly, the quantitative characteristic of reliability is the probability R of the non-failure operation in the given interval of time, $R(t) = P(\tau > t)$, where τ is a random value of time of the failure-free operation. Another important characteristic of reliability is the so-called hazard or failure-rate function, $\lambda(t) = -R'/R$, which has the meaning of the conditional probability of failure per unit time provided the device operated failure-free up to the given moment. With time, when wear-out of functional elements comes into play, the failure rate of the device begins to grow up (period of wear-out failures) [3].

How to create a reliable system from unreliable components which experience permanent fluctuations? Of course, thermal fluctuations become essentially lower if a device can operate at helium temperatures. The alternative way of achieving the high systems reliability while dealing with unreliable components is to learn wisdom by the examples of Nature.

2 MALFUNCTIONS OF BIOLOGICAL CONSTRUCTIONS

Similarly to technical devices, biological devices are not perfectly reliable in operation: malfunctions happen alternating with normal operation functions [4-6]. The simplest biological device is enzyme, the function of which consists in catalyzing a specific biochemical reaction. From the point of view of engineering, an enzyme is actually a "robot" specialized in accelerated assembly and disassembly of specific molecules. At present, there is a conception regarding the enzyme catalytic mechanism according to which the catalysis is performed as a process of step-by-step electron-conformation interactions, which are induced by attachment of the substrate molecule to the enzyme molecule [7]. The sequences of electron-conformation interactions represent the displacements and reorientations in enormous quantities of atomic groups. Therefore, temperature and other fluctuations bring about

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random accidents in the sequences of electron-conformation interactions, i.e. the possibility of conformational relaxation changes in an "incorrect" direction. Such accidents develop in one or another functional violation of the enzyme (inactivation, violation of selectivity, etc.), i.e. in failure. Thus, the conformational fluctuations set limits to reliability of enzymes.

Energetic demands of every operation in living systems are met by molecules of adenosine triphosphate (ATP) which are synthesized from adenosine 5'-diphosphate (ADP) and inorganic phosphate (P_i). Most of ATP is produced in the special organelles of cells, the so-called mitochondria. Therefore, a mitochondrion exemplifies the biomolecular nanoreactor of primary importance. There are specific enzymes organized in the respiratory electron transport chains (ETC) in the inner membrane of the mitochondrion. Each ETC consists of four lipoprotein complexes (I–IV), coenzyme Q which operates as an electron shuttle between complexes I/II and III, and cytochrome C as the electron shuttle between complexes III and IV [8].

Normal functioning of the ETC's enzymes lies in the transport of electrons, one by one, from the electron donor molecules ("oxidative substrates", NADH/succinate) on the chain to the end enzyme, cytochrome oxidase of complex IV, from which the electrons are transferred to molecules of oxygen with two-electron reduction of oxygen into water. Free energy released during the electron transport is used in complex V for synthesis of ATP from ADP and P_i by oxidative phosphorylation [8].

The mitochondrial enzymes have very ancient evolutionary origin and, hence, seem to be ones of the most reliable molecular machines. But yet their reliability characteristics are not perfect because these molecular machines experience conformational fluctuations. In consequence, normal elementary acts of the electron transport alternate with random malfunctions at complexes I and III when an electron, rather than waits for transport to the next enzyme of ETC, goes directly to an adjacent oxygen molecule resulting in production of superoxide free radical ($O_2^{\bullet -}$). Meanwhile, chemical products of $O_2^{\bullet -}$, the so-called reactive oxygen species (ROS), are toxic and initiate free-radical damages in the biomolecular nanoreactors. Therefore, the malfunctions in ETC followed by production of $O_2^{\bullet -}$ are considered as the failures of vital importance for living cells [4-6].

The chloroplast of green plants exemplifies another case of malfunctions. The main functional elements of the chloroplast nanoreactor are molecules of chlorophyll, the derivatives of Mg-protoporphyrin complexes. Chlorophyll molecules (Chl) are specifically arranged in pigment protein complexes which are embedded in the lipoprotein thylakoid membranes of chloroplasts. The function of the vast majority of Chl (antenna Chl) is to absorb light and transfer that light energy by resonance energy mechanism to specific energy sinks, the reaction centers of the chloroplast nanoreactor photosystem I and photosystem II. Eventually, the light energy is used by the enzyme components of the thylakoid membrane electron transport chains for synthesis of ATP and NADPH which are thereafter employed for synthesis of carbohydrates and so on [8]. Similarly to the mitochondrial nanoreactor, normal electron transport alternates with random malfunctions resulting in generation of $O_2^{\bullet -}$ [6, 8].

While performing their function, the light-exited antenna Chl molecules are in the singlet state ^{1}Chl (electron spin $S = 0$). However, there is the probability of order 10^{-4} of the radiationless relaxation into the triplet state ^{3}Chl ($S = 1$) followed by the chemical reaction with oxygen

$$^3\text{Chl} + {}^3\text{O}_2 \rightarrow \text{Chl} + {}^1\text{O}_2$$

in which singlet oxygen $^1O_2$ evolves [8]. Thus, normal functioning of the antenna chlorophyll is attended by production of $^1O_2$. The $^1O_2$ molecules are essentially more reactive than usual triplet O_2 molecules and initiate photodynamic damages followed by inactivation of the biomolecular nanoreactor. Therefore, the "erroneous" relaxation of ^{1}Chl attended by production of $^1O_2$ should be considered as the malfunction (failure) of the antenna chlorophyll device.

3 RELIABLE SYSTEMS FROM UNRELIABLE COMPONENTS

There are several lines of creating reliable biological devices from unreliable components. One of them is redundancy, when redundant components of the same type are introduced in the system to fulfill one and the same function. There are different kinds of redundancy, among them - structural (insertion of superfluous amount of functional elements), functional (exploitation of the elements capable to carry out additional functions besides their basic), informational (surplus information), temporal (superfluous time of functioning). For example, all essential biomolecular constructions are present in cells in superfluous amounts. The redundant amounts of enzymes, mitochondria, chloroplasts, and other organelles represent the examples of the structural and functional reservation.

Another line of enhancement of reliability is to supply the possibilities of repair of damaged components. However, when a functional element is replaced once its failure or damage takes place, the failure rate may become intolerably high. In order to decrease the failure rate of the system its elements should be replaced before they become wearout or damaged. Indeed, renewal processes proceed in all complex biological systems, starting from the cell level. The DNA/RNA template synthesis, the so-called turnover, provides the preventive maintenance replacement of cell components. This preventive replacement of functional elements, which follows the pattern preset in the cell genome, is the main line of providing the high reliability of biological systems despite low reliability of cell functional elements, enzymes and so on [4-6].

In mitochondria, there is a specific antioxidant enzyme, the so-called superoxide dismutase (mtSOD), the function of which is to trap $O_2^{\bullet-}$. This enzyme catalyzes the reaction of dismutation of $O_2^{\bullet-}$ into hydrogen peroxide (H_2O_2) and oxygen (O_2) thus protecting cell structures from $O_2^{\bullet-}$ and its toxic chemical products. It makes its defense "job" in cooperation with two other specific enzymes, catalase and glutathione peroxidase, which catalyze decomposition of H_2O_2 into H_2O and O_2. Thus, the antioxidant enzyme system provides the preventive maintenance against the active forms of oxygen.

The calculations, based on the experimental data and the "Birth and Death" model, often used in the mathematical theory of reliability, show that the rate parameter for the "free-radical failures" of ETC in normal mitochondria $\lambda \approx 0.25\ s^{-1}$ (about 1 radical every 4 s). The rate parameter for elimination of $O_2^{\bullet-}$ by SOD (probability of elimination of one $O_2^{\bullet-}$ per unit time):

$$\mu \approx -\Delta n(t)/n(t)\Delta t = k_e[E] \approx 1.3\cdot 10^4\ s^{-1}.$$

Here $n(t)$ is the number of $O_2^{\bullet-}$ in a mitochondrion, $\Delta n(t)$ is the number of the radicals eliminated during the time interval Δt, k_e and $[E]$ are the reaction rate constant and the concentration of mtSOD, respectively. Then the probability of slipping of $O_2^{\bullet-}$ through the mtSOD defense has been estimated to be:

$$z = (\lambda/\mu)/(1+\lambda/\mu) \approx 1.9\cdot 10^{-5}.$$

Thus, only 2 radicals from every 100,000 may penetrate the defense system. Nonetheless, it was estimated that the longevity of human brain could reach 250 years, should the reliability of the mitochondrial nanoreactors and the reliability of the antioxidant enzyme defense be absolutely perfect [4-6].

In the photosynthetic nanoreactors of chloroplasts, apart from superoxide dismutase which trap $O_2^{\bullet-}$, there is another special antioxidant system, the so-called carotenoids ("xanthophylls"), which trap $^1O_2$. The reactivity of carotenoids, such as β-carotene, lycopene, zeaxanthin, with singlet oxygen is characterized by the rate constants of the diffusion order, of $3\cdot 10^{10}\cdot L\cdot M^{-1}\cdot s^{-1}$. The carotenoids effectively catch the $^1O_2$ molecules thereby preventing photodynamic damages of biomolecular components in the chloroplast nanoreactor.

4 PREVENTIVE MAINTENANCE VIA SPIN-CATALYSIS

Beyond the energy control, any chemical reaction as electron-nuclear rearrangement of reactants into products is controlled by angular momentum (spin) of reactants. The reaction is rigorously forbidden if it requires a change in total electron spin, a spin evolution, of the reactants. To lift the ban, spins of the reactants must be changed. The acceleration of the spin evolution and the relevant acceleration of the reaction may be performed via spin-catalysis, be it an external magnetic field ("magnetic field effect"), interaction with unpaired electrons of external paramagnetic ions and free radicals ("electron spin catalysis"), or hyperfine coupling with magnetic nuclei ("magnetic isotope effect") [9].

The general theory of spin catalysis forecasts that spin moments of magnetic nucleons can afford preventive antioxidant effects in nanoreactors. The currently available data suggest that it takes place with regard to the nuclear spin moment of magnesium-25.

Amongst three stable magnesium isotopes, ^{24}Mg, ^{25}Mg and ^{26}Mg, only ^{25}Mg has the nuclear spin (I). It has been recently discovered that the rate of oxidative phosphorylation of ADP in cell mitochondria with magnetic nuclei ^{25}Mg ($I = 5/2$) is about twice higher than that with the spinless, nonmagnetic nuclei ^{24}Mg or ^{26}Mg ($I = 0$). There was no difference between $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ effects in oxidative phosphorylation [10]. It is well-known that oxidative phosphorylation is a complex multi-step reaction [8]. The observations made by Buchachenko and his co-authors demonstrate that a rate-limiting step in oxidative phosphorylation is a spin-selective process, a certain intermediate ion-radical pair, the spin evolution of which is catalyzed by the magnetic isotope. It may be the adenine anion-radical of ADP, bound in the ATP-synthase active center and coupled with the ETC's cation ("hole"), as it was first suggested in our paper [7], or it may be the intermediate ion-radical pair of $[ADP]^{\bullet-}$ with Mg^+ cation, as it was proposed in [10, 11].

No matter what the spin evolution, the catalytic effect of the magnetic ^{25}Mg isotope transpires that phosphorylation of ADP should proceed essentially slower when nucleus of Mg^2+ has no spin magnetic moment than in the case when nucleus of Mg^{2+} has the spin magnetic moment. The retardation of oxidative phosphorylation causes the relevant delay in transport of electrons through the ETC enzymes. While the input of the mitochondrial nanoreactor is overflowed with electrons, it increases probability of the malfunction in the nanoreactor with one-electron reduction of oxygen and formation of radical $O_2^{\bullet-}$. As a result, the yield of $O_2^{\bullet-}$ as the by-product of electron transport in the mitochondrial nanoreactor is bound to be much lower in the presence of ^{25}Mg-ADP by comparison with ^{24}Mg- or ^{26}Mg-ADP. In essence, magnesium-25 exerts the preventive antioxidant effect. Hence, the magnetic isotope can perform the preventive maintenance against the active forms of oxygen, thereby providing the higher system reliability [12].

Quite the reverse, prooxidant, effect of magnetic ^{25}Mg is to be exerted in the case of antenna chlorophyll of green plants. Firstly, the nuclear spin of ^{25}Mg can catalyze the radiationless conversion of photoexited chlorophyll molecules into the triplet state ^3Chl (electron spin $S = 1$). Secondly, it can significantly accelerate the above mentioned reaction of the triplet chlorophyll with oxygen in which the singlet $^1O_2$ oxygen evolves. Indeed, the pair of

initial reactants, ^{3}Chl and $^3O_2$, has total electron spin $S = 2$ and five spin states which correspond to spin projections $S_z = \pm 2, \pm 1, 0$. On the other hand, the pair of products, Chl and $^1O_2$, has total spin $S = 0$. Hence, out of five possible spin state of the reactants there is a single state from which the reaction is open (permissible). Other four "channels" of the reaction are spin-forbidden since the total electron spin of the system must have been changed in the course of the reaction. Consequently, there is little likelihood of significant rate even though this reaction may be catalyzed by spin-orbital or spin-rotational coupling.

However, slow or no spin evolution of the reactants can be accelerated by the nuclear spin of magnesium-25. As a result, one can expect for the essentially higher yield of $^1O_2$ and, thereafter, essentially more the $^1O_2$ induced photodynamic damages of biomolecular components in photosynthetic nanoreactors when chlorophyll molecules contain ^{25}Mg instead of the spinless ^{24}Mg or ^{26}Mg. Thus, in the chloroplast nanoreactor, the nuclear spin catalyst should decrease the system reliability [12].

5 SUMMARY

Functional elements of molecular dimensions in nanoengineering devices are susceptible to environmental fluctuations. That raises the question as to whether operation of the nanoscaling devices can be reliable. One can lower temperature up to helium values at which thermal fluctuations are less. The alternative way is to follow the general theory of reliability and bionics. Insertion of redundant amount of the functional nanocomponents, which fulfill one and the same function, magnifies the system reliability. Another line of creating the highly reliable systems from unreliable components is preventive maintenance or prophylaxis of failures.

Keeping in mind the possible free-radical damages, researchers who fabricate new composite materials embedded with organic dye molecules, metal atoms, and nanoparticles should provide them with appropriate antioxidants as well.

In design of reliable spin-dependent molecular devices for optical communications, quantum information processing, computational schemes and the like, stable magnetic isotopes hold much promise. Moreover, along this nanoengineering line the general principles of spin-chemistry, amongst them – control of chemical reactivity by selective isotope modification and relevant microwave variations, can be employed in optoelectronic and nanophotonic devices.

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