Blood analysis for early cancer detection

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Abstract

The interaction between the nuclear quadrupole moments of ions and the electric field gradient in a biological membrane can explain the mechanism of active transport in cells. On the basis of a model, we discuss the NMR isotopic analyzer of blood for the detection of cancer without exposing the patient to any radiation. The method involves a low temperature technique.

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1 Introduction

We propose an explanation for the active transport in biological cells by a model based on quadrupole interactions between nuclei of ions and electric field gradients in membranes. It has shown that isotope analysis of blood are needed for testing cancer and its mutations. The method involves a technique used for polarized targets [1]. It consists of the following steps [2]:
1. Cooling down a sample of blood in order to freeze molecular motions.
2. Beam irradiation of the sample to induce electron F-centers.
3. Dynamic nuclear polarization (DNP) at $0.1 \div 1$ K in a magnetic field.
4. Analysis of the isotopic composition by Nuclear Magnetic Resonance (NMR).
This fundamental research is necessary to better understand the behavior of various diseases, while medical trials and studies provide crucial information on the effect of therapies.

2 Simplified motivation of the method

We consider blood as liquid tissue consisting of plasma (55%) and blood cells suspended in plasma. Plasma provides the circulation of blood but plays also another role. It is mostly water (92%) which has a complex dielectric permittivity with a real part $\epsilon' \approx 50 \div 80$ and a considerable value of the imaginary part ϵ'' or a large energy attenuation. As a consequence, the

plasma decreases the effect of external electric fields on cells. This is a first important physical property which is inherent to the structure of blood.

The blood cells include red cells, white cells and platelets. The major chemical elements of cells are given in Table 1. One can see that nuclei of cells have small γ-gyromagnetic ratios, as compared to hydrogen (^{1}H) in the plasma. Consequently, they weakly interact with magnetic fields, so that we can exclude an influence of magnetic interactions on cells.

All cells are enclosed in structures called membranes. A membrane defines a separated space in which cells may maintain a chemical environment that

Table 1: **Major chemical elements composed the blood.**

Nucleus	Spin	γ	Q	ν	P_i *in* 2.5 T	*Field* $[T]$	J_p/J_i
		$[MHz/T]$	10^{-24} cm^2	$[MHz]$	[%]	$\nu = 10^7$ Hz $[Rel.\ Un.]$	
^{1}H	1/2	42.57	0.	106.4	51.	0.235	1.
^{14}N	1	3.078	0.020	7.695	5.5	3.25	900
^{16}O	5/2	5.774	-0.026	14.43	18	1.73	31
^{31}P	1/2	17.25	+0.0	43.12	22	0.579	14
^{33}S	3/2	3.272	-0.076	8.18	7.3	3.056	400
^{13}C	1/2	10.71	+0.0	26.77	14	0.934	57
^{35}Cl	3/2	4.176	-0.0825	10.44	9.3	2.394	190
^{127}I	5/2	8.578	-0.79	21.44	26	1.166	10
^{23}Na	3/2	11.27	0.104	28.17	24	0.887	10
^{39}K	3/2	2.006	0.049	5.015	4.5	4.986	1700
^{25}Mg	5/2	2.608	0.201	6.52	8.1	3.834	340
^{43}Ca	7/2	2.869	-0.049	7.172	11	3.485	140
^{55}Mn	5/2	10.53	+0.33	26.35	31	0.949	5
^{63}Cu	3/2	11.30	-0.211	28.25	24	0.885	10
^{65}Cu	3/2	12.103	-0.195	30.25	26	0.826	8

differs from the outside. There are two ways in which substances can enter or leave a cell: a) the passive way (diffusion and osmosis) which requires no energy from the cell, b) the active way which is the energy-demanding transfer of a substance across a membrane. Passive transport moves particles (atoms, ions or molecules) from an area of higher concentration to an area of lower concentration. Active transport moves ions across cell membranes from an area of lower concentration towards an area of higher concentration. This active transport is contrary to what would be expected and is the main goal of our further consideration.

At equilibrium, between the inner and outer sides of a cell appear two concentration gradients of ions which create a charge separation and the so-called "resting" membrane voltage

$$\varphi \;=\; \varphi_{in} - \varphi_{ext} \approx -80\ mV, \tag{1}$$

where φ_{in} and φ_{ext} and φ are the internal and external potentials and the resting voltage on a membrane, respectively. In turn, the resting voltage creates an electric field in a membrane. Strength of this field depends on the shape and thickness of membrane.

Excitation of resting voltage by neuron impulses causes a transition to the new spatial geometry of electric field in membranes. Heat exchange between cells and plasma can be a reason of deformations of cells shape. Any reshaping of electric field provide energy needed for active transport due to nuclear quadrupole interactions of ions with emergent gradient of electric field in membranes. We consider here an active transport of sodium and potassium ions under the influence of quadrupole interactions.

3 Quadrupole "sodium-potassium pump"

The electric field in a membrane is the force (F) which is exerted on the charge (q). The resting voltage from Eq. 1 excites in membrane a field (E) of the order of

$$E \;=\; \frac{F}{q} = -\frac{\partial\varphi}{\partial z} = -\varphi_z \approx -\frac{\varphi}{\Delta z} \approx \frac{80\cdot 10^{-3}}{8\cdot 10^{-9}} \approx 10^5\ [V/m], \tag{2}$$

where $\Delta z \approx 8\cdot 10^{-9}\ m$ is the approximate thickness of a membrane. The excitation of a resting voltage causes a transition to a new value of equilibrium concentrations of ions. This excitation cannot be attributed to an interaction between the electric field and dipole moments of nuclei since atomic nuclei do not have measurable electric dipole moments. Since the atomic mass of ions is mainly concentrated in their nuclei, we consider only the interaction between nuclear quadrupole moments and the electric field gradient in a membrane. For simplicity, the energy of an interaction (W_q) between nuclear quadrupole moment and the electric field gradient can be written as [3]

$$W_q \;=\; \frac{eQ}{4}\cdot\frac{\partial E}{\partial z} = -\frac{eQ}{4}\cdot\frac{\partial^2\varphi}{\partial z^2} = -\frac{eQ}{4}\cdot\varphi_{zz}, \tag{3}$$

where φ_{zz} is the electric field gradient in a membrane, eQ is the nuclear quadrupole moment, e is the elementary charge, Q is given in Table 1. We

assume the axial symmetry of the field gradient and a moment. According to Table 1, the nuclei of cells possess the significant values of quadrupole moments. The force of quadrupole interaction (F_q) acting on a nucleus is

$$F_q = \frac{\partial W_q}{\partial \varphi_{zz}} \cdot \frac{\partial \varphi_{zz}}{\partial z} = -\frac{eQ}{4} \cdot \frac{\partial \varphi_{zz}}{\partial z} = M_i \cdot a_i, \quad (4)$$

where, from the second Newton's law a_i is acceleration of the ion i produced by a force (F_q) acting on a mass M_i. In our case M_i is the mass of the ion i crossing a membrane. It is clear from Eq. 4 that a quadrupole pump can work while the field gradient (φ_{zz}) is changed across membranes. Using Eq. 4 and Table 1, we obtain a relation between the sodium (a_{Na}) and potassium (a_K) accelerations at equal field gradients in a membrane

$$a_{Na} = \frac{Q_{Na}}{Q_K} \cdot \frac{M_K}{M_{Na}} a_K = \frac{0.104}{0.049} \cdot \frac{39}{23} a_K = 3.6 \cdot a_K. \quad (5)$$

Hence, the acceleration by the forces of active transport is by a factor of 3.6 higher for sodium ions than for potassium ions. Therefore, if $F_q < 0$ means that sodium ions are leaving a cell, for the same time interval, potassium ions maintain their higher concentration inside cells. At point $\partial \varphi_{zz}/\partial z = 0$, the active transport stops running ($F_q = 0$), upgrading concentrations and resting voltage. Since φ_{zz} does not depends on z-axis inversion, the pump can move ions to both sides by inverting the sign of $\partial \varphi_{zz}/\partial z$. The motion of other ions could be considered by the similar way. It is clear however, that the isotope composition of cells have an extremely flexible mechanism for its adaptation to an environment.

Our analysis shows, that the operation of a sodium-potassium pump depends first on the concentrations of isotopes in blood needed for a passive transport and secondly on the response of active transport for a cell excitation. Thus, the isotopic imbalance should point to a violation of metabolic processes in cells and can be a reliable marker for the detection of cancer.

4 Practical remarks

The isotopic composition of blood can be better examined at low temperatures using the technique of polarized target [1]. For the proposed study, it takes a sample of about $3 \div 4$ cm^3 of blood frozen at 90 K. The cooling freezes the molecular motions and converts the liquid into an amorphous structure with a random spatial distribution of spins. Equiprobable distribution in

space allows us to calculate the line shape and electric field gradients.
Nuclei with half-integer spin have NMR spectral line on the Larmor frequency. These frequencies in a field of 2.5 T are listed in the ν-column of Table 1. Assuming that DNP implies equal spin temperature for all nuclear species, we show in Table 1 the polarizations of isotopes (P_i) in a field of 2.5 T at 4.4 mK spin temperature, as calculated by the Brillouin formula. This spin temperature corresponds to proton polarization of 51%, which is unlikely to be practically achieved in such complex substances as blood.

Below 0.2 K, the nuclear relaxation times can reach many hours and the nuclear polarizations "are frozen". It is then possible to compare intensities of spectral lines at fixed frequency of a receiver by adjusting the magnetic field to a partial isotope resonance. In this case the ratio of integral intensities for two spectral lines v_p and v_i equals to [4]

$$\frac{\int_0^\infty v_p(\omega)d\omega}{\int_0^\infty v_i(\omega)d\omega} = \frac{N_p}{N_i} * \frac{I_p\gamma_p^2}{I_i\gamma_i^2} * \frac{P_p}{P_i} = \frac{N_p}{N_i} * \frac{J_p}{J_i}, \tag{6}$$

where N_p and N_i are spin densities, the index p stands for proton spins (^{1}H) and i for other isotopes, $P_{p,i}$, $I_{p,i}$, $\gamma_{p,i}$ are the nuclear polarization, spin, gyromagnetic ratio, respectively. Table 1 gives the resonant fields for the central line of isotopes (see column "$Field\ [T]$") and the ratio J_p/J_i - of integral intensities for a fixed frequency of $\nu = 10^7\ Hz$ at N_p=N_i.

Our analysis shows that optimal isotope analyzer should operate at $1 \div 4$ K temperature range in a field of about 5 T. It should have a pair of RF-coils, one for protons of plasma and the other for the nuclei of cells.

5 Conclusion

We have elaborated a model of active transport in biological cells based on the quadrupole interaction between nuclear quadrupole moments of ions and the electric field gradient in a membrane. For simplicity, the angular part of quadrupole energy was not considered. At equal field gradients in membrane, the acceleration by the forces of active transport is a factor of 3.6 higher for sodium ions than for potassium ions. Unlike diffusion and osmosis, the active transport using the quadrupole interaction can change the direction of ions by inverting the sign of the electric field gradient $\partial\varphi_{zz}/\partial z$. Isotopic imbalance in blood means a violation of metabolic processes in cells and it can be a reliable marker for detecting cancer development. For applications, we have estimated parameters of a NMR analyzer for the cancer diagnostic.

References

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