

Electrophoretic Mobility of Cell Nuclei (EMN) index – relation to biological and physical properties of the cell

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Abstract

The authors describe certain physical and biological properties of cell and resulting electrical and electrokinetic properties, directly or indirectly related with the Electrophoretic Mobility of Cell Nuclei (EMN) index. This index, may become a new criterion in the estimation of the biological age, irrespective of the stage of the ontogenesis.

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Introduction

A research is conducted in the Institute of Anthropology of Adam Mickiewicz University on the assessment of human biological age using the Electrophoretic Mobility of Cell Nuclei (EMN) index. As evident from the studies, the value of the EMN index grows in the progressive phase of the ontogenesis, to fall markedly with age after the organism has reached biological maturity. This physico-chemical phenomenon is based on the facts that cellular nuclei oscillate in a variable electrical field, and that proportions of the number of cells with oscillating nuclei to the number of cells with non-oscillating nuclei change in the course of the ontogenesis. Finding out the ratio of the number of cells with os-

cillating nuclei to the number of cells with non-oscillating nuclei (per 100 cells counted by the researcher, with a proper ratio of the size and colour of the nucleus to the size of cytoplasm maintained) allows determining the percentage value of the EMN index. The EMN index is determined with the use of human buccal epithelium tissue.

An anthropologist or auxologist studying the phenomenon of Electrophoretic Mobility of Cell Nuclei (EMN) usually neglects the biophysical aspect of the phenomena under investigation and is usually interested in the final effect that he needs to obtain in his research, namely in the percentage value of the index. In this paper we would like to describe certain physical and biological properties of the cell and the resulting electrical and electrokinetic properties directly or indirectly related with the electrophoretic mobility of cells and oscillating cell nuclei.

Electrical properties of the cell

Electrical properties of a given substance in varying states of aggregation depend on two fundamental physical quantities: 1) conductivity (for an anthropologist the term resistivity or resistance will be more understandable), and 2) permittivity. These two parameters have values characteristic for each substance and show varying dependency on the frequency of the electromagnetic field in which they are measured, i.e. they have different dispersion values. The two above-mentioned parameters depend on temperature and usually have temperature change coefficients characteristic of particular substances. Here, one should point out that the resistivity of a given substance is determined by the type and concentration of free charges present in this substance and by the conditions of their movement upon the application of the electric field. Electrical permittivity, on the other hand, depends on the spatial distribution of charges tied in atoms or particles and on the degree of their ability to shift one another in the electric field.

Taking into account the fact that it is a cell in the electrical field that is an object observed in the EMN phenomenon, it is understandable that certain current must flow through this cell. For the current flow to occur free electrical charges or ions must be present. Even clean water dissociates, and as a result, conducts electrical current. The cytoplasm in a cell is just a colloidal water solution. In water being a component of cytoplasm the salts, acids and bases dissociate exceptionally strongly. Therefore, even small admixtures of these substances result in the increase of conductivity.

In other words, taking into consideration certain physical characteristics the interior of a cell can be considered a multi-phase colloidal system made up of a variety of protein molecules, nucleic acids, fats, carbohydrates, water, a certain number of small-particle organic compounds and mineral salts.

In the process of the carrying of electric current the cytoplasm behaves as a complex electrolyte or even suspension in which certain components constitute electrolytic dispersive environment and the others the dispersed phase. The electric conductivity of this substance depends on the concentration of particular types of ions and on their mobility. Small ions (such as K^+ , Na^+ , Cl^-) play the most active part in conductivity since they are very mobile, while macromolecules, on the one hand, are responsible for the weakening of the external field and for hydrodynamic retardation of the mobility of fast ions as well.

With respect to electrical conductivity, the cell membrane is an insulator. This property of the membrane owes mainly to the lipid layer. Together with intra and extracellular molecules the membrane forms an electrical capacitor, which contributes the reactive component to the impedance of a cell, that is to the resistance of a cell with respect to the alternative current flowing through this cell.

Due to these properties the cell undergoes the so-called ionic interspatial polarisation in the electric field. In other words, the cell behaves like a huge dipole, because a great number of ions, closed in the cell with its cytoplasmatic membrane cannot leave it and in this way a dipole is formed.

The above-described properties of the cell suggest certain conclusions to as in

relation to the observed EMN phenomenon. Placing cells in the low frequency electric field (1–2 Hz in the EMN research) results in the flow of current. It is known from the literature [TERLECKI, KOTARSKI 1985], that as a result of high electrical resistance of the membrane in these low frequencies ions inside of the cell undergo separation and a strong dipole is induced. For this reason the value of permittivity is very high, but all lines of current omit the cell. The increase of frequency is accompanied with gradual decline of this effect. At adequately high frequencies (approximately 20 MHz) capacitance resistance of the membrane encompasses only the resistance of the lipid layer. As a result the intracellular substance participates in the conduction of current. The ionic polarisation of the cell fades away.

Recapitulating, the effect of the oscillation of cell nuclei may result also, but not only, from the fact that though the cell as a whole is strongly resistant, at increased frequency of the electric field its resistance declines. Relating this fact to the percentage share of oscillating nuclei in the total number of nuclei observed in the ontogenesis, we may conclude that at a constant frequency of the electric field which was applied in our study the cells of young individuals are more resistant, i.e. they offer higher resistance to the current in comparison with the cells belonging to older individuals. More cells have oscillating nuclei because older cells are less resistant so they offer less resistance to the electric current flowing through them. Obviously this variability of the EMN index, does not result solely from the physical properties of the cell undergoing changes in the course of ontogenesis, but also in-

directly from changing properties of biological membranes, which will be shown further in the paper.

Electrokinetic properties of cell

Apart from water solutions of electrolytes in a cell we have to do also with colloidal solutions, i.e. suspensions or emulsions. These solutions are made up of very tiny particles of solid bodies, liquids or gas bubbles dispersed in liquid medium. In an ultra-micro-non-homogeneous system, such as, for instance, our human buccal epithelium cell under observation, we distinguish at least two phases: dispersed and continuous one. On the surface of the charged particles of dispersed phase, ions (opposite charge) adsorb in the form of a tight envelope. The charges of the particle itself and of the layer of ions clinging to the surface of the particle form an electrical double layer inside of which the potential has a linear course. In a certain distance from the surface ionic particles with the same sign as the adsorbed ions form the next diffuse layer. In this layer the potential does not change in a linear manner along with the distance. The value of the potential that stabilises at the borderline between the double and the diffuse layer is called electrokinetic potential and is denoted by ζ zeta. Most often it is called simply the zeta potential. The existence of the electric double layer and zeta potential is responsible for the occurrence of the so-called electrokinetic phenomena, such as electroosmosis, electrophoresis, the streaming potential and the Dorn effect.

Due to the specific character of our research we will briefly describe the phenomenon of electrophoresis. Typical electrophoresis consists in the movement

as a result of the application of the electric field of charged particles of diffuse phase relative the stationary dispersion medium. When particles are charged positively, they travel to the cathode (cataphoresis), while particles with negative charge migrate to the anode (anaphoresis). Electrophoresis makes it possible to determine the charge of particles and the value of electrokinetic zeta potential. The latter is to be calculated from the equation

$$\zeta = \frac{k\eta\mu}{\epsilon E}$$

where

η denotes viscosity, ϵ the permittivity of dispersion medium, μ the mobility of particles, E the electric field intensity, and k is a coefficient dependent on particle shape ($k=4$ for cylindrical particles, and $k=6$ for spherical ones).

The electrokinetic zeta potential plays a significant role in biological systems and has been known for a relatively long time. Yet still there are no satisfactory results of the research on this phenomenon. Nevertheless, it is known for instance that it prevents agglutination of erythrocytes. Also, due to zeta potential erythrocytes are pushed to the lumen of a blood vessel, which reduces friction. On the basis of the above equation the parameter μ describing the mobility of particles in electrophoresis can be calculated. At this moment we would like to discuss the aspect of electrophoretic mobility with regard to cells and nuclei, that is the aspect which directly describes the EMN phenomenon.

Electrophoretic mobility of cells and cell nuclei

The notion of electrophoretic mobility of cells (μ) in biology was probably in-

troduced for the first time by Helmholtz and Smoluchowski [MAYHEW, NORDLING 1968]. Authors proposed a physical formula describing this phenomenon:

$$\mu = \frac{\zeta\Sigma}{4\pi\eta} = \frac{\sigma\chi}{\eta}$$

where

ζ is the zeta potential, Σ the dielectric constant of the medium at the electrophoretic shear layer, η the viscosity of the medium at the electrophoretic shear layer, σ the charge density of the cell surface, and χ some effective thickness of the ionic double layer surrounding the surface.

If throughout the duration of the experiment the conditions are stable resulting the constant value of parameters χ , η , Σ , then electrophoretic mobility of cells and cell nuclei is directly proportional to the zeta potential and to the density of charge on the cell surface and it does not depend on the size. At the same time this means that in the cells and in isolated nuclei the charge density on their surface is the same. The work by MAYHEW, NORDLING [1968] corroborates also speculations on the increase of charge density along with the increase of the intensity of metabolic processes. This entails other consequences too, such as the fact that the density of charges increases in the cells after an operation on a part of liver. In these cases, in the regenerating cells with increased metabolism gradual increase in mobility is observed see Table 1. Similar phenomena are observed in young, developing rats metabolising with greater intensity than adult animals. The charge on their epithelium is higher and as a result they have greater cell mobility. The below diagram in Fig. 1 clearly confirms the dependencies observed in the EMN phenomenon. As shown in the diagram, the mobility of young cells is approxi-

mately 42% higher than the mobility of liver cells of adult rat. The diagram indicates also that the mobility of these cells decreases in the course of the post-natal growth.

Table 1. Changes in the electrophoretic mobility of animal liver cells after partial hepatectomy [EISENBERG ET AL. 1962]

Number of animals	Period after operation [h]	Average electrophoretic mobility [cm/Vs]
20	0	0.97
3	0,5	1.11
2	2	1.20
4	6	1.25
3	12	1.26
4	24	1.22
6	48	1.28
3	72	1.17
3	21 days	0.98

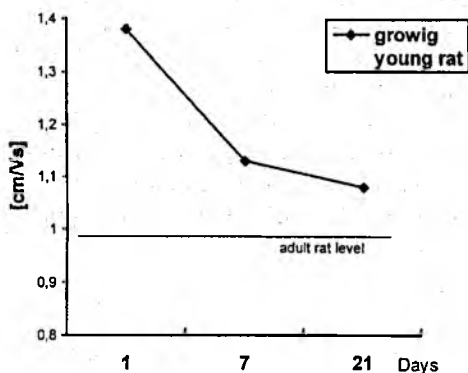


Fig. 1. Changes in electrophoretic mobility of liver cells in the course of the ontogenesis of young rats [EISENBERG ET AL. 1962]

Observing human buccal epithelium cells under the microscope we follow the course of specific electrophoresis, where negatively charged cells migrate in the direction of the positive end or anode (anaphoresis) [SHAKHBAZOV 1986]. It is obvious then that in this case the cell behaves like a giant macromolecule (dispersed substance) in the dispersion medium of 0,09% NaCl solution [MAKAŁOWSKA 1992]. Reading the

works from the 1960s describing the EMN phenomenon one comes to think that that is where the phenomenon under discussion derives from. The very specific character of the method and the mathematical formula of the EMN index is based simply on the percentage share of cells with oscillating nuclei in relation to the share of cells with non-oscillating nuclei. Thus, the Electrophoretic Mobility of Cell Nuclei is nothing else but the migration of the human buccal epithelium cells (in our study) in the electric field. It should be noted that from the point of view of the very methodology of EMN this aspect is neglected with the whole attention focused on the effect of macro-oscillating nuclei.

It is interesting that the surface of a cell usually has a negative charge [MAEKAWA 1967]. For this reason the research on the EMN phenomenon indicates that whole cells migrate towards the anode. It is also interesting that malignant cells have a much higher negative charge, which results in their varying electrophoretic mobility [EISENBERG 1962, AMBROSE 1956]. As far as nucleus is concerned, it was established [MAEKAWA 1967] that the increase in the density of the charge on its surface corresponds exactly to the DNA replication period and, in consequence, to the increase of active metabolism connected with the synthesis of RNA and proteins. This is obviously reflected in the properties of the surface of cell cytoplasmatic membrane because of the connection of cytoplasmatic membranes of the cell with plasmatic membranes surrounding the nucleus. However, the relationships of the cell and nucleus mobility with their metabolism are still a matter of discussion. Studies [KISHIMOTO, LIEBERMAN

Table 2. Influence of temperature on electrophoretic mobility of the liver cells of an adult rat [EISENBERG *ET AL.* 1962]

Number of animals	Temperature [°C]	Time of heating [min]	Mean mobility [cm/Vsec]	Percentage increase in mobility
6	27	—	0.98	100
3	60	30	0.95	97
2	65	10	1.39	142
4	70	10	1.65	168
3	96	30	1.65	168

1965] seem to corroborate relationship between intense metabolic processes (replication of DNA) and the properties of nuclear membranes, and as a result with electrophoretic mobility.

In hepatic cells no difference in the mobility of island forming type and free cell type of cells was observed [MAEKAWA 1967]. This fact is significant from the methodological point of view of the research on the EMN phenomenon. We avoid the island forming cells and count only free ones. In the research on the electrophoretic mobility of mouse liver cells and isolated homogenous liver cell nuclei [MAYHEW, NORDLING 1968] no differences between average values of mobility were found, though among various types of cells such differences occurred. Average values of the mobility of mouse liver cells did not differ significantly (statistically significantly) for various mice.

To conclude the discussion on the electrokinetic properties and resulting electrophoretic mobility of cells and isolated cell nuclei, we would like to present two diagrams explaining in what way pH and temperature affect the mobility of cells (Fig. 2 and Table 2). This is directly related to the research and methodology concerning the EMN, since the change in the electrophoretic mobility of cells must entail changes in the number of oscillating nuclei. Gradual decreasing (Fig. 2) of pH till approximately 5.4 does not entail significant changes in mobility. When pH is further

decreased below this value till the isoelectric point of approximately 4.0, being more or less the isoelectric point of the majority of proteins, a sharp drop in mobility is noted. Further decrease of pH results in the reversion of the value of the charge. Heating to the temperature (Table 2) exceeding 60 °C does not cause significant changes in the electrophoretic mobility of cells. At 65 °C a 42% increase in mobility is observed. Further heating results in 68% increase of mobility, but heating to the temperature exceeding 70 °C does not cause any further changes in the electrophoretic mobility. An assumption can be made that at a certain value of temperature (between 60–70 °C) the mobility stops changing.

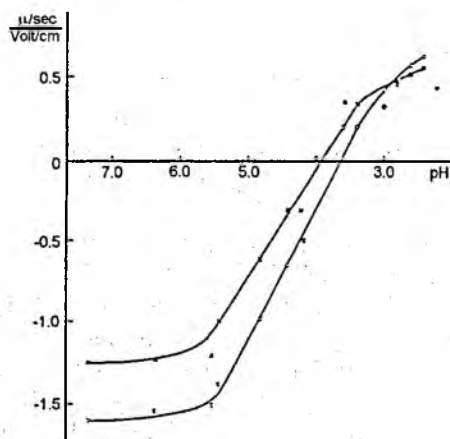


Fig. 2. Effect of pH on electrophoretic mobility of normal liver cells and regenerating cells of an adult rat (48 hours after the operation, crosses – normal cells, dots – regenerating) [EISENBERG *ET AL.* 1962]

Ageing of biological membranes and its relationship with EMN

The ageing of cells and biological membranes is a vast topic and for the lack of room it cannot be discussed in this paper in detail. However, we will try to present at least certain biological processes taking place with time in ageing membranes in the context of electrical and electrokinetic properties of the cell, we described earlier. To this end we will make use of the works of the authors of the EMN method published in the 1990s.

As we know, cellular membranes of various types depending on which organelle they are part of (plasmatic membrane, membrane surrounding mitochondrion, endoplasmic reticulum or nuclear areola) differ with their structure and (to a lesser degree) with chemical composition. Functionally, we can distinguish two categories of plasmatic membranes. One category is related to the permeation of various substances to and from the cell, the other one is responsible for enzymatic properties, it fulfils enzymatic functions. According to MAEKAWA [1967] these properties of cellular membranes decide about the electrophoretic mobility of cell nuclei. Intramolecular systems are closely interconnected. As a result, a damage to one of biological processes taking place in some isolated part of a cell affects other processes, causing a number of disturbances. Mechanisms responsible for damages to cells are sometimes difficult to describe, but most often one of the four intracellular systems becomes damaged. The four systems are: oxygen respiration system, cellular membrane system or systems maintaining the functions of cellular membranes (mainly synthesising phospholipids); system of the syn-

thesis of enzymes and structural proteins and genetic apparatus repair systems [ZABEL 1995]. There is evidence that transporting properties of the cellular membrane, e.g. properties related to the functioning of the sodium-potassium pump change with age.

SHOKORBATOV [1995a, 1995b] and his team conducted research that indirectly corroborated relationships between the changing with age EMN index and the degree of biological membranes degradation being an effect of biological ageing processes. In order to prove that, he introduced indigo carmine into buccal epithelium cells of individuals in various phases of ontogenetic development. The results of these studies are shown in Table 3.

Table 3. Differences in the stainability of cells depending on their age [SHOKORBATOV *ET AL.* 1995a*, 1995b]

Age	Number of subjects	EMN [%]	Stainability of cells [%]
19-22*			57.8 ± 4.4
40-56*			81.9 ± 2.6
69-80*			89.5 ± 2.2
19-24	21	66.1 ± 2.9	68.7 ± 4.2
40-56	12	46.3 ± 3.8	80.4 ± 2.2
69-82	10	40.4 ± 4.2	87.2 ± 2.8

Upon the analysis of the above table and diagram one can easily draw the following conclusions: Staining of the cells with indigo carmine in the course of ontogenesis changes differently to the changes in the EMN index. In the stable and involutinal phases of the ontogenesis the index correlates negatively with the stainability diagram. This is a clear corroboration of the fact that with age cells increase their permeability for certain substances for which they were not permeable in the earlier phases of ontogenesis. In reference to electrical properties discussed at the beginning of this paper, one can say that with age a cell

transports more free ions, which means that deteriorated cellular membrane is less resistant (has lower resistivity). Properties of the EMN phenomenon with regard to cellular membranes have their origin also in the changes occurring with age in the nucleus and they refer to DNA as well as to its interactions with chromatin proteins. These interactions are electrostatic in character and their strength depends on the charge and conformation of proteins. The reason behind such reactions in the nucleus is not quite clear. There is a theory that a change in the ionic environment of nucleoplasma is the cause. It has been confirmed that quantity of some ions in the cell nucleus increases with age.

Conclusions

The EMN phenomenon, still only partly explained, is related to the biochemical composition and physiology of cellular structures as well as to the properties of physical and chemical nature or with electrokinetic and electrostatic properties of nuclei and other cellular structures undergoing change with age. This results mainly but not only, from the degradation of protein-lipid membranes. The degree of the degradation increases with age and manifests itself in their increased permeability, which can be related indirectly to the decreasing values of the EMN index in the stable and involutinal phases of the ontogenesis. To conclude, we would like to point out to the fact that there are also studies providing explanation for the EMN phenomenon at the cytogenetical, biochemical and physiological levels which has not been referred to in this work. We would like to add that we are trying to explain the es-

sence of the EMN phenomenon employing the methods of spectrometry of nuclear magnetic resonance (NMR), and thus at a submolecular or even atomic level [CZAPLA, FOJUD 1998; in press].

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Streszczenie

Od kilku lat w Instytucie Antropologii Uniwersytetu im. Adama Mickiewicza w Poznaniu prowadzone są badania nad wykorzystaniem wskaźnika elektroforetycznej ruchliwości jąder komórkowych (EMN – Electrophoretical Mobility of Cell Nuclei) do oceny wieku biologicznego w dowolnej fazie ontogenezy. Stwierdzono, że w trakcie ontogenezy zmieniają się proporcje pomiędzy ilością komórek, które – obserwowane w trakcie elektroforezy – charakteryzują się ruchliwymi jądrami do komórek, których jądra się nie poruszają. Procentowy stosunek liczby komórek z jądrami poruszającymi się, do komórek z jądrami nieruchomymi określa procentową wartość wskaźnika EMN.

W zjawisku EMN obserwowanym obiektem jest komórka nabłonka jamy ustnej w polu elektrycznym. W procesie przewodzenia prądu elektrycznego cytoplazma wykazuje cechy złożonego elektrolitu lub nawet zawiesiny, w której jedne składniki stanowią elektrolityczne środowisko dyspersyjne, a inne – fazę rozproszoną. Przewodność elektryczna cytoplazmy zależy od koncentracji poszczególnych rodzajów jonów i ich ruchliwości; największy udział w przewodności mają jony małe (np. K^+ , Na^+ , Cl^-). Błona komórkowa jest pod względem przewodnictwa elektrycznego izololatorem. Błona łącznie z substancją wewnątrz- i zewnątrzkomórkową stanowi kondensator elektryczny, który wnosi składową bierną do impedancji komórki, czyli oporu komórki wobec przepływającego prądu. Komórka w polu elektrycznym ulega tzw. polaryzacji jonowej – międzyprzestrzennej i zachowuje się jak olbrzymi dipol. Umieszczając komórki w polu elektrycznym o małej częstotliwości (w badaniach EMN 1–2 Hz) powodujemy przepływ prądu. Wiadomo z literatury [TERLECKI, KOTARSKI 1985], że przy niskich częstotliwościach następuje, na skutek dużego oporu elektrycznego błony, separacja jonów we wnętrzu komórki i zostaje indukowany wspomniany wcześniej silny dipol. Z tego powodu wartość przenikalności elektrycznej jest bardzo duża, ale wszystkie linie prądu omijają komórkę. Ze wzrostem częstotliwości efekt ten stopniowo maleje. Przy odpowiednio wysokich częstotliwościach (około 20 MHz) opór pojemnościowy błony zawiera tylko opór warstwy lipidowej, w związku z czym substancja wewnątrzkomórkowa bierze udział w przewodzeniu prądu, a polaryzacja jonowa komórki całkowicie zanika. Reasumując możemy powiedzieć, że efekt drgania jąder komórkowych wynikać może między innymi z faktu, że komórka jako całość stawia opór czyli jest silnie rezystentna; gdy zwiększymy częstotliwość jej rezystencja maleje. Odnosząc to do zmian procentowego udziału drgających jąder obserwowanych w ontogenezie możemy wnioskować, że przy stałej częstotliwości pola elektrycznego jakie stosuje się w badaniach, komórki osobników młodszych są bardziej rezystentne czyli stawiają większy opór przepływającemu prądowi w porównaniu z komórkami osobników starszych i dlatego więcej komórek ma jądra drgające. Zmienność wskaźnika EMN wynika nie tylko z właściwości fizycznych komórki, które ulegają zmianie w ontogenezie ale również, pośrednio, ze zmieniających się właściwości błon biologicznych.

Obserwując komórki nabłonka błony śluzowej jamy ustnej pod mikroskopem obserwujemy przebieg specyficznej elektroforezy. Ujemnie naładowane komórki migrują w stronę anody [SHAKHBAZOV 1986]. Podstawę oznaczania EMN jest więc migracja komórek (w naszym przypadku nabłonka jamy ustnej) w polu elektrycznym, przy czym ten aspekt zjawiska z punktu widzenia metodyki EMN jest pomijany, zwraca się bowiem uwagę na efekt makro – drgających jąder. Związki ruchliwości jąder i komórek z ich metabolizmem pozostają nadal w sferze dyskusji. Badania KISHIMOTO i LIEBERMANA [1965] wydają się potwierdzać związek między intensywnością procesów metabolicznych (replikacja DNA) a właściwościami błon jądrowych i tym samym z elektroforetyczną ruchliwością.

Fenomen zjawiska EMN – nie do końca wyjaśniony – związany jest z właściwościami elektrokinetycznymi i elektrostatycznymi jąder i innych struktur komórkowych, które wraz z wiekiem ulegają zmianie. Jest to wynik, między innymi, degradacji błon białkowo-lipidowych. Wzrasta ona z wiekiem i przejawia się zwiększoną ich przepuszczalnością co można pośrednio wiązać ze zmniejszającymi się wartościami wskaźnika EMN w stabilnej i inwolucyjnej fazie ontogenezy.