EQUATIONS USED IN INTRODUCTION OF THE CONCEPT OF RESTING MEMBRANE POTENTIAL IN MODERN TEXTBOOKS OF HUMAN PHYSIOLOGY: TRADITIONS AND ALTERNATIVES

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Abstract. In the system of medical education physiology is a discipline of key importance based on very dynamic field of scientific knowledge. Permanent emergence and accumulation of new facts and concepts make teaching of physiology challenging task where success and effectiveness are highly dependent on abilities of teaching staff and authors of textbooks constantly to evaluate, re-evaluate and improve teaching approaches, learning objectives and sometimes even to revise whole paradigms in organizing and prioritizing essential parts of the curriculum. Resting membrane potential (RMP) is a concept of critical importance in physiology and particularly in physiology of excitable structures. Equations quantitatively characterizing RMP are widely used in teaching practice as a tool bridging the gap between fundamental biophysical phenomena and complex physiological processes. Use of different equations in introduction of the concept of RMP in modern teaching literature is studied and critically evaluated. Alternative approaches are discussed in search for improvement and optimization of traditional methods of teaching resting membrane potential in courses and textbooks of human physiology. Study is based on the review and content analysis of different editions of more than 25 modern textbooks of human physiology.

Keywords: medical education; physiology teaching; resting membrane potential; Goldman equation; Mullins-Noda equation; chord-conductance equation; sodium-potassium pump

Introduction

Physiology is a highly dynamic and permanently evolving field of scientific knowledge. Accumulation of facts, emergence of new concepts and revision of old ones occurs at rates without precedents in the history of physiological science and particularly human physiology. Taking into account typical duration of modern professional life-span (exceeding 40 years), development of scientific knowledge seems to be extremely accelerated not only in historical perspective but also on the level of personal professional development of scientists, teaching staff and authors of textbooks. In these circumstances teaching physiology as a basic discipline is a specific and challenging task.

As a result of constant ‘delay’ of teaching practice from the research frontlines, continuously widening gap exists between the physiology as a science and physiology as an academic discipline. It causes progressing failure of teaching process and textbooks to encompass and rationally integrate in its ‘body’ permanent developments in scientific knowledge and to present it in accordance with constantly evolving educational needs of medical students.

Although there is a general consensus among the academic communities that it is normal and beneficial (at least for natural sciences) disciplines to stay behind scientific frontiers, there are no established criteria allowing reliable judgments to be done about the acceptable size of the ‘gap’ between science and discipline and when it is above or below the ‘normal’ ranges. If the delay between appearing of important scientific facts and concepts and their incorporation in the textbooks and curriculums is measured in years, there are no ‘guidelines’ saying that, for example, periods of 5, 10, 20 or 50 years are acceptable or not. Therefore, it is highly specific and problematic task to assess whether the information presented in structure and content of the curriculums and textbooks adequately reflects scientific progress and, more importantly, evolving educational needs of the students. In such circumstances permanent dialogue and discussions between teaching staff, biomedical scientists and healthcare professionals are vitally important for achieving optimal results in educational process and keeping on-track physiology as an academic discipline.

Effective teaching practice, bringing stable and long-lasting results, requires from teaching staff and authors of teaching literature faculties of critical thinking which are vitally important in permanent evaluation, revision and systematic analysis of the curriculum and bringing it up-to-date together with the content and structure of physiological courses. Frequently under scrutiny must be placed not mere facts and concepts but whole deeply-rooted paradigms in methodology of physiology teaching. This processes, of course, also affect content, structure and quality of all accompanying teaching materials and textbooks.

Introduction of resting membrane potential (RMP) in modern courses and textbooks of physiology is one of the most illustrative examples of disparity between physiology as a discipline and physiology as a science. A remarkable diversity of approaches and solutions in teaching literature is a clear symptom of critical lack of consensus among the authors in defining and characterizing RMP – basic concept of key importance in almost all branches of modern physiology and especially physiology of excitable structures.

Traditionally, RMP is taught by use of equations which are beneficial in pointing out basic factors determining its quantitative characteristics. First equation derived to quantify specifically RMP (or V_m) in a multi-ion environment is published in 1949 by Hodgkin and Katz. It is based on the assumptions of Goldman (1943) that electric field across a cell membrane is constant and that net ionic current (sum of individual ion currents - $I_{Na^+}, I_{K^+}, I_{Cl^-}$) across the cell membrane equates zero, Eq. (1). So nowadays it is known as Goldman-Hodgkin-Katz equation (GHK) or simply as Goldman equation.

$$I_{Na^+} + I_{K^+} + I_{Cl} = 0 \tag{1}$$

In teaching literature GHK is presented in two forms – classical, Eq. (2) and simplified, Eq. (3):

$$V_m = 61\ lg \frac{P_{K^+}[K^+]_e + P_{Na^+}[Na^+]_e + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_e} \tag{2}$$

$$V_m = 61\ lg \frac{P_{K^+}[K^+]_e + P_{Na^+}[Na^+]_e}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i} = 61\ lg \frac{[K^+]_e + \frac{P_{Na^+}}{P_{K^+}}[Na^+]_e}{[K^+]_i + \frac{P_{Na^+}}{P_{K^+}}[Na^+]_i} \tag{3}$$

where P_{K^+}, P_{Na^+} and P_{Cl^-} are membrane permeabilities for the individual ions; $[K^+]$, $[Na^+]$ and $[Cl^-]$ are extracellular (index *e*) and intracellular (index *i*) molar concentrations of respective ions. At the time of publication of GHK nothing was known about the active transport mechanisms (and particularly Na^+/K^+ pump) and ion channels, which existence was hypothesized in the mid-50s (Hodgkin & Keynes, 1955).

The deriving model of both forms of GHK is not strictly applicable in evaluation of RMP of a normal living cells as no allowance is made for active transport (discovery of sodium-potassium pump was reported by Skou (1957) - almost ten years after the article by Hodgkin and Katz) thereby contradicting constant intracellular ion concentrations at physiological steady state (Eq. (1)).

Alternative and much more intelligible to students of medicine way of expressing RMP is by chord-conductance equation (CC):

$$V_m = \frac{g_{Na^+}E_{Na^+} + g_{K^+}E_{K^+} + g_{Cl^-}E_{Cl^-}}{g_{Na^+} + g_{K^+} + g_{Cl^-}} \tag{4}$$

where $E_{Na^+}E_{Na^+}$, $E_{K^+}E_{K^+}$ and $E_{Cl^-}E_{Cl^-}$ are equilibrium potentials of the ions; $g_{Na^+}g_{Na^+}$, $g_{K^+}g_{K^+}$ and $g_{Cl^-}g_{Cl^-}$ are respective ion conductances of cell membrane. CC is easily derived on the ground of Eq. 1 and Ohm's law using ion conductances instead of resistances. Frequently in CC Cl^- are omitted (as is the case of simplified form of GHK) because if V_m is close or equal to E_{Cl^-} contribution of Cl^- is negligible.

Discovery of Na^+/K^+ pump (Skou, 1957) and establishing its stoichiometry made possible effect of the active ion currents to be taken into account. Among the proposed equations best fitted for teaching purposes of physiology is that derived by Mullins & Noda (1963) because of its relative simplicity, similarity to Nernst equation, and direct account of electrogenic effect of Na^+/K^+ pump:

$$V_m = 61\,lg\frac{rP_{K^+}[K^+]_e + P_{Na^+}[Na^+]_e}{rP_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i} = 61\,lg\frac{r[K^+]_e + \frac{P_{Na^+}}{P_{K^+}}[Na^+]_e}{r[K^+]_i + \frac{P_{Na^+}}{P_{K^+}}[Na^+]_i} \quad (5)$$

where r reflects Na^+/K^+ pump stoichiometry (r = 3/2=1,5). The role of Cl^- is again neglected for the same reasons as in the cases of simplified GHK and CC. GHK is based on the assumption of flux steady state (Eq. (1)), whereas the Mullins-Noda equation (MN) applies to the assumption of concentration steady state. Last one can be expressed in the following way:

$$I_X^p + I_X^a = 0 \quad (6)$$

where I_X^p and I_X^a are passive and active currents of each individual ion X across the cell membrane. Although much more restrictive than assumption in equation 1, assumption in equation 6 matches with cell's real and physiological steady-state where ion concentrations are kept constant. Therefore, resemblance between simplified GHK, Eq. (3) and MN, Eq. (5) is just a formal one as they are based on completely different assumptions of steady state (*cf.* Eq. (1) and Eq. (6)).

Aims and methods

The aim of the study is to identify, quantify and critically analyze (mainly from didactical point of view) equations used in introduction and characterization the concept of RMP in modern teaching literature of medical physiology.

Study covers 50 editions of 28 titles in the field of human physiology addressed to a medical students or future medical students. Selection of the literature was based on three main considerations: (1) in order to be reflected current tendencies in teaching approaches and practices year of publication of selected editions is not earlier than year 2000; (2) well known and widely used titles with more than 1 edition were preferentially included in the study; (3) Some of the titles were included because of their specific innovative and contributing approach to the subject of RMP.

Most of the editions are in English language, but teaching literature in Russian, Italian and Bulgarian languages is also presented.

Results

Results of the analysis are summarized in Table 1. In regard to the equations used in teaching RMP as a basic concept in physiology, six distinct approaches were identified.

Most of the authors from the selected sources prefer classical form of the GHK, Eq. (2). RMP is introduced with Eq. (2) by the authors of 18 editions of 10 leading textbooks (36% of the sampled titles). Second and much smaller group of authors (representing 3% of the titles) introduces RMP with the help of simplified form of GHK, Eq. (3). There is a special case in the referred editions of textbooks by Boron and Boulpaep where simultaneously three equations are mentioned in details – both forms of GHK, Eqs. (2) and (3) and CC, Eq. (4). In general, GHK, Eq. (2) and/or (3) is presented in 21 editions of 12 textbooks (43% of the selected titles).

Table 1. Summary of different approaches involving equations used in Introduction of the concept of RMP in modern teaching literature of human physiology

Equation	References	Editions (titles)
1. Classical form of Goldman-Hodgkin-Katz (GHK) $V_m = 61\,lg\frac{P_{K^+}[K^+]_e + P_{Na^+}[Na^+]_e + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_e}$	Conti, 2004; Ganong, 2001, 2003; Pocock & Richards, 2006; Guyton & Hall, 2005, 2011, 2016[1] (Ed. 11, 12, 13); Rhoades & Tanner, 2003 (Ed. 2); Rhoades & Bell 2009, 2013 (Ed. 3, 4); Boron & Boulpaep, 2012, 2016 (Ed. 2, 3); Silverthorn 2010, 2013 (Ed. 5, 6); Vander et al., 2000 (Ed. 8); Vander's 2003[2], 2008[3], 2014[4] (Ed. 9, 11, 13)	18 (10)
$V_m = 61\,lg\frac{P_{K^+}[K^+]_e + P_{Na^+}[Na^+]_e}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i}$	Johnson, 2003; Boron & Boulpaep 2012, 2016 (Ed. 2, 3); Sherwood, 2010, 2016	5 (3)

$V_m = \frac{g_{Na^+}E_{Na^+} + g_{K^+}E_{K^+} + g_{Cl^-}E_{Cl^-}}{g_{Na^+} + g_{K^+} + g_{Cl^-}}$	Berne et al., 2004, 2008[5] (Ed. 5, 6); Costanzo, 2006, 2010, 2014, 2018 (Ed. 3, 4, 5, 6); Boron & Boulpaep, 2012, 2016 (Ed. 2, 3); Raff & Levitzky, 2011; Kibble & Halsey, 2009	10 (5)
4. Gibbs-Donan $V_m = P_{Na^+}E_{Na^+} + P_{K^+}E_{K^+} + P_{Cl^-}E_{Cl^-}$	Despopoulos & Silbernagl 2003, 2009[6] (Ed. 5, 6); Brown, 2012 (Ed. 2)	3 (2)
$V_m = 61\,lg\frac{r[K^+]_e + \alpha[Na^+]_e}{r[K^+]_i + \alpha[Na^+]_i}$	Yankov, 2007, 2011;	2 (1)
6. Without equation	Alipov, 2013; Sudakov, 2000; Smirnov, 2002; Tkachenko, 2005; Ganong, 2005, 2010[7], 2012[8], 2016[9]; Sherwood, 2012; Fox, 2004, 2011, 2016 (Ed. 8, 12, 14)	12 (7)
Total, titles (editions):		50 (28)
[1)]Hall, 2016; [2)]Widmaier et al., 2003; [3)] Widmaier et al., 2008; [4)]Widmaier et al., 2014; [5)]Koeppen & Stanton, 2008; [6)]Silbernagl & Despopoulos, 2009; [7)]Barrett et al., 2010; [8)]Barrett et al., 2012; [9)]Barrett et al., 2016.		

The second place in the rating of popularity among the authors is occupied by CC, which is the main and most preferred alternative to GHK. It is used by 10 editions of 5 textbooks (36% of the titles).

In the fourth approach presented in table 1 concept of RMP is unconventionally introduced by the help of modified form of Gibs-Donan equation (3 editions of 2 titles).

A unique solution among the sampled teaching literature is demonstrated by Yankov (2007; 2011). The author uses MN (Eq. 5) to explain RMP and participation of active ion currents in setting cell's steady state.

A well established and growing tendency among the authors is giving up any equations at all when the concept of RMP is introduced (25% of the titles). Especially pronounced is this trend among the Russian-language authors (100% of the Russian language textbooks in the sample).

Discussion

Results of the study clearly demonstrate lack of consensual approach among the authors of teaching literature towards the RMP and role of equations in its introduction. The approaches used by modern authors vary in the broad range where in one end is classical form of GHK (first equation derived for calculation of membrane potential in multi-ionic environment) while in the other one is complete exclusion of equations quantifying RMP (Table 1). Established diversity in the approaches of the authors toward such fundamental concept in physiology as RMP can be regarded as a clear sign of discrepancy (or even conflict) between physiology as a dynamically growing field of scientific knowledge and physiology as an academic discipline. The last one is a function not only of a scientific knowledge as such and its dynamic progress but also of constantly evolving educational needs of the medical students. In brief, physiology as a discipline is placed on the cross point of science and education.

Despite the limitations of GHK, Eq. (2) and its principal incompatibility with steady-state of normal living cells (Eq. (1) and Fg. 1), analyzed literature clearly demonstrate that it is a most favorable equation among the majority of the authors. From didactic point of view advantages of GHK are its generic similarity to Nernst equation (well known to medical students after introduction of the concept of equilibrium potential) and pointing out the key role of selective ion permeability of the cell membrane in determining value of RMP. Changing ion permeability serves as an important explanatory device when graded and action potentials are discussed later. Additional didactic advantage of simplified form of GHK, Eq. (3) is its focus on Na^+ and K^+ – most important players in processes of membrane depolarization and repolarization and main 'substrates' of Na^+/K^+ pump.

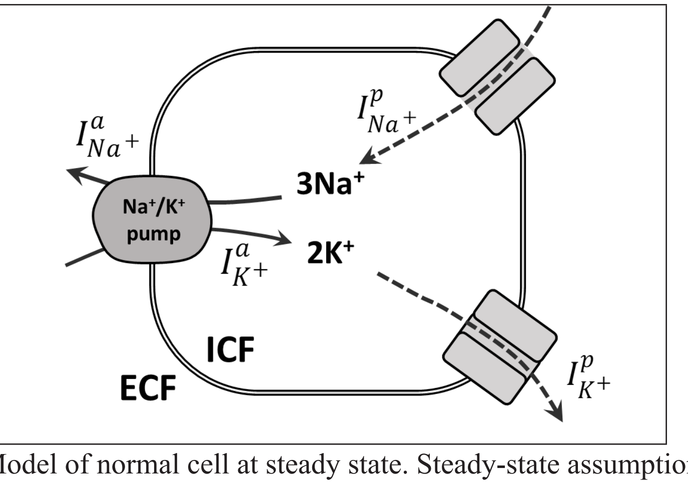

Figure 1. Model of normal cell at steady state. Steady-state assumption of GHK counts only passive currents (dotted arrows, Eq. (1)) regarding cell as Na^+ 'black hole' and K^+ 'white hole'. Concentration steady state model of MN is based on the much more restrictive assumption of balance between active (I^a) and passive (I^p) currents for each individual ion, Eq. (6). ICF and ECF – intra and extracellular fluid

CC (the second most popular equation, Eq. 4) and Gibbs-Donan equation (Table 1) also suffer from the same common problem deeply rooted in the model of flux steady state, Eq. (1). Almost all equations in use take into account only passive transmembrane currents. In only one textbook from the sampled literature is used Mullins-Noda equation which is derived on the ground of stoichiometry of Na^+/K^+ pump and model of concentration steady state based on the assumption that active and passive currents are in balance for each individual ion, Eq. (6). In regard to RMP there is an interesting paradox in modern teaching literature of physiology which is almost totally dominated by the equations which by their nature are not physiological but pathophysiological. In fact, they were derived to reflect adequately conditions in which Na^+/K^+ pump is blocked directly or indirectly (for example, when in pathophysiological states ATP synthesis is suspended). From didactical point of view, the role of such equations in teaching physiology is severely limited by their neglect of Na^+/K^+ pump – the structure ultimately involved in generating and maintaining RMP. Probably this is one the major reasons (together with will of many to escape from any complicated physical and mathematical concepts) why in the past few decades growing amount of authors prefer to explain RMP without any equations.

Among the equations in Table 1 CC is unique as it is derived from Millman's (1940) theorem which in turn is rooted in Ohm's law and first law of Kirchhoff. CC is gaining popularity in the past few decades thanks to its simplified mathematical form and the fact that laws of Ohm and Kirchhoff are well known to majority of the students. Additional advantage of CC in teaching process is the way it is derived which can easily be demonstrated and understood by the students of medicine. Also, very useful are direct links existing between the concept of electrochemical gradient, Ohm's law and CC.

MN is presented in only one textbook from analyzed teaching literature. It is amazing that equation published in 1963 and having all advantages of GHK and being free of its fundamental limitations (from physiological and didactical point of view) still has no place in teaching literature of physiology. Even more amazing is the fact that much more authors prefer to exclude from their texts any equations than to introduce MN. Two main specific advantages of MN should make it sound alternative to GHK: relative simplicity (in comparison with equations like that proposed by Moreton (1969) and smooth integration with the key themes of Na^+/K^+ pump and steady-state of real normal cell.

Although common 'thermodynamic' roots of GHK and MN and their similarity with Nernst equation provide some advantages in teaching process, they constitute a substantial source of troubles arising from relatively complicated mathematical shape of GHK and MN and the fact that medical students (and frequently teaching staff and authors of textbooks themselves) lack systematic knowledge about basic concepts of mathematics and thermodynamics to comprehend these equations. As a result, they and models staying behind them are just memorized without being understood. In this circumstances CC offers far more intelligible alternative but still on the prize of sacrificing physiological model of cell's steady state.

Is it possible advantages of MN and CC to be combined, but without their inherent didactical limitations? Although not presented in the selected sample of teaching literature, such alternative exists. Stoichiometry of Na^+/K^+ pump can be 'incorporated' successfully in the CC taking into account following ratio between Na^+ and K^+ currents (I_{Na^+} and I_{K^+}) across the cell membrane (Fig. 1).

$$\frac{I_{Na^+}}{I_{K^+}} = \frac{3}{2} = -1{,}5 \tag{7}$$

Minus sign in the equation indicates opposite directions of I_{Na^+} and I_{K^+}. In steady state active and passive currents for each individual ion are balanced (eq. 6) so the equation 7 can be applied for both of them. Expressing ion currents through their respective ion conductances and electrochemical gradients (in accordance to Ohm's law) Eq. (7) can be transformed in the following steps:

$$\frac{g_{Na^+}(V_m - E_{Na^+})}{g_{K^+}(V_m - E_{K^+})} = -1{,}5 \tag{8}$$

$$g_{Na^+}(V_m - E_{Na^+}) = -1{,}5\, g_{K^+}(V_m - E_{K^+})$$

where $E_{Na^+}E_{Na^+}$ and $E_{K^+}E_{K^+}$ are Nernst equilibrium potentials of Na^+ and K^+. Solved for the RMPl last equation takes this form:

$$V_m = \frac{1{,}5 g_{K^+}E_{K^+} + g_{Na^+}E_{Na^+}}{1{,}5 g_{K^+} + g_{Na^+}} = \frac{1{,}5E_{K^+} + \frac{g_{Na^+}}{g_{K^+}}E_{Na^+}}{1{,}5 + \frac{g_{Na^+}}{g_{K^+}}} \tag{9}$$

Last equation is based on relatively simple and well-known concepts of Ohm's law and first law of Kirchhoff, main advantage of CC, and accounts active ion currents driven by Na^+/K^+ pump – main didactic advantage of MN over GHK.

Conclusion

Analyzed sample of modern teaching literature of human physiology clearly demonstrate that introduction of the concept of RMP most frequently is done through equations (mainly GHK and CC) that are incompatible with the modern concept of concentration steady-state of normal cell. They neglect active ion currents and particularly the role of Na^+/K^+ pump which makes them ineffective of presenting basic mechanisms involved in creating and maintaining RMP of real normal cells. Although much better alternatives to GHK and CC are available, Eqs. (5) and (9), which successfully overcome inborn limitations of GHK and CC, they still have no adequate application in teaching process and remain excluded from the mainstream of teaching literature of human physiology. Some deeply rooted traditions of teaching RMP in physiology courses and textbooks for medical students need profound revision and optimization.

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