Response of the gravito-inertial mechanoreceptors during a fall: a mathematical model

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Abstract. Various types of vestibular prosthesis prototypes have been developed as an aid for treatment of equilibrium disturbances. One of the primary tasks for improving these prosthetic devices is the development of output stimulating impulses that may resemble the natural response of the vestibular system. In this work, a mathematical model of the information output from the gravito-inertial mechanoreceptor of the vestibular apparatus is presented. For this, we have considered five compartments: mechano-electrical transduction, adaptation of transduction, hair-cell ionic current, synaptic transmission, and afferent neuron discharge. The numerical parameters of the model were obtained from experiments that were done in the inner ear of the rat. The results of the numerical analysis of the model showed that the mathematical modelling may be used to construct an encoder system for the artificial sensors (micro-accelerometer) contributing to the development of a reliable vestibular prosthesis prototype.

1 Introduction

The vestibular system, as well as other sensory organs, is a complex structure in which optimization of incident energy to impinge and stimulate specific sensory cells takes place. In the vestibule, the semicircular canals and the otolithic organs allow the perception of the influence of gravity and of inertial forces produced by changes of the head position to provide information used to stabilize the gaze and the posture.

Receptor hair cells of the vestibular system convert the energy of a mechanical stimulus and transmit information about it to the first afferent neurons and then to the central nervous system. The functional scheme of the vestibular mechanoreceptor is

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shown in Figure 1. Displacement of the sensory hair bundle activates the transduction process that originates a transducer ionic current. This leads to potential change in the cell membrane that activates various voltage- dependent ionic channels in the hair cell. This series of events finally produces a voltage- dependent activation of calcium channels, and the subsequent activation of the neurotransmitter release machinery leading to synaptic activation of the afferent neurons in the vestibular nerve. The primary afferent neurons integrate the activity from various synaptic sources and accordingly generate a series of action potentials. These afferent impulses are the output from the vestibular mechanoreceptor. In the scheme (Figure 2) two levels of control are taken into account: intrinsic based on the mechanism of adaptation of the transducer current and extrinsic based on the operation of the efferent innervation.

In this work, we present a compartmental model of the vestibular mechanoreceptor in which we have considered five compartments: mechano-electrical transduction, adaptation of the transduction mechanism, hair cell ionic currents, synaptic transmission, and afferent neuron discharge. In relation to the control mechanism, we only considered the adaptation of the transducer mechanism. In this paper we consider the union of the mathematical models that were presented earlier as a gravito-inertial mechanoreceptor mathematical model.

2 Mathematical Model

Let us examine the extreme situation: initial stage of the uncontrolled fall of a man in the sagital plane (during 100 ms), when there is still a possibility of the vertical pose stabilization. As shown [2], the greatest reaction of hair cells to the mechanical stimulus, which leads to the fall, occurs for the cells situated along the axis of the sensitivity of the macula of sacculus, orthogonal at the local vertical line at the initial moment of the fall (Fig. 1).

The sacculus, just as the utriculus, is a multi-dimensional accelerometer that makes it possible to obtain information about the apparent acceleration of the otolith membrane from many directions of sensitivity. Only one of these directions interests us, as mentioned above. In connection with this, we will not consider the mathematical model of the dynamics of the whole otolith membrane on the plane that is parallel to the plane of the macula, and the response to this stimulus of many hair cells and primary afferent neurons, but only the dynamics along the axis of sensitivity that was determined above. Hair cells located along the considered axis of sensitivity (Fig. 1), in which the positive direction coincides with the direction of the forward fall (they are located before the striola – reversal line), and the hair cells in which the positive direction coincides with the direction of the backward fall (they are located after the striola), we will consider the reactions of two hair cells with opposite polarity. We have designated the hair cell altogether with the primary afferent neuron as vestibular mechanoreceptor.

The term "gravito-inertial mechanoreceptor" for the stabilization of the vertical

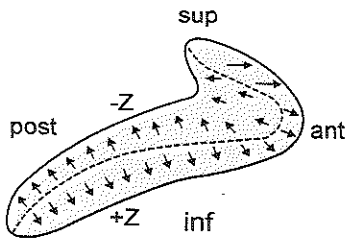

Fig. 1. Functional polarity of the sacculus hair cells.The striola is designated by the dotted line. Arrows represent the direction of maximal sensitivity for hair cells (Spoendlin H.H. In: Wolfson R.J.,ed. The vestibular system and its diseases. Philadelphia, 1966, University of Pennsylvania Press)

position will be used to name the set of the three mathematical models: the first of them describes the dynamics of the displacement (x_s) [3] of the otolith membrane along the axis of sensitivity that is being considered, and the other two models describe the response of the mechanoreceptors of the opposite directions sensitivity ($x=\pm x_s$) of the otolith membrane (Fig. 2).

In sections 2.1 and 2.2 the basic model consisting of the "Current dynamics in hair cells" and "Afferent neuron dynamics" are presented. In section 2.3 these two blocks are connected by the "Synaptic transmission" block. Also described are the input of the "Mechanoelectrical transduction" and the "Transducer adaptation" to prolonged mechanical stimulus.

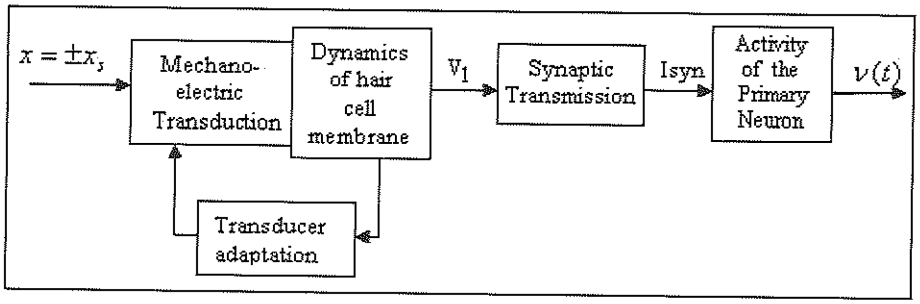

Fig. 2. Scheme of the vestibular mechanoreceptor compartments considered in the model.

2.1 Current dynamics in hair cells

The model is based on the Hodgkin-Huxley equations. This is a simplified model, assuming that the dynamics of a hair cell may be described using a single total ionic current I_T [1], where I_T is the sum of the principal currents of the hair cells. The model is summarized in (1).

$$
\begin{gathered}
C_{m1}\frac{dV_1}{dt} = -I_{Tr} - I_T - I_{L1}, \quad I_T = g_T m^3 (h_1 + h_2)(V_1 - E_T), \quad I_{L1} = g_{L1} V_1, \\
\tau_m(V_1)\frac{dm}{dt} = m_{ST}(V_1) - m, \\
\tau_{h_1}(V_1)\frac{dh_1}{dt} = q_1 h_{ST}(V_1) - h_1, \\
\tau_{h_2}(V_1)\frac{dh_2}{dt} = q_2 h_{ST}(V_1) - h_2,
\end{gathered}
\tag{1}
$$

Here I_T is the total ionic current; m is the parameter that specifies the current activation process; h is the parameter that specifies the current inactivation process; g_T is the maximum conductance; I_L is the leakage current; and I_{com} is, under natural conditions, the current flowing into a hair cell through the transduction channels ($I_{com} = -I_{Tr}$), or in the experiments, the command current. The inactivation parameter h has two constituents ($h=h_1+h_2$) corresponding to the potassium channels with fast and slow inactivation time constants. Functional parameters are shown in table 1, where $m_{\min}$, $h_{\min}$, $\tau_{\min}$, $\tau_{\max}$, V_{ac}, V_τ, V_h, S_{ac}, S_r and S_h are coefficients of sigmoidal fitting curves that containing this functional parameters; k_{h1}, k_{h2}, b_{h1}, b_{h2} are coefficients of approximation for the fast and slow inactivation time constants.

Table 1. Functional parameters of the model used in (1)

Name	Functional Form	Name	Functional Form
Steady-state Activation	$m_{ST}(V_1) = m_{\min} + \dfrac{1 - m_{\min}}{1 + \exp\left(\dfrac{-(V_1 - V_{ac})}{S_{ac}}\right)}$	Fast Inactivation Time Constant	$\tau_{h1}(V_1) = k_{h1}V_1 + b_{h1}$
Activation Time Constant	$\tau_m(V_1) = \tau_{\min} + \dfrac{\tau_{\max} - \tau_{\min}}{1 + \exp\left(\dfrac{V_1 - V_\tau}{S_\tau}\right)}$	Slow Inactivation Time Constant	$\tau_{h2}(V_1) = k_{h2}V_1 + b_{h2}$
Steady-state Inactivation	$h_{ST}(V_1) = h_{\min} + \dfrac{1 - h_{\min}}{1 + \exp\left(\dfrac{V_1 - V_h}{S_h}\right)}$		

Table 2. Hair cell numerical parameters.

Parameter	Semicircular Canal	Parameter	Semicircular Canal	Parameter	Semicircular Canal
C_{ml}	11.26 *pF*	S_τ	15.68 *mV*	V_h	-9.82 *mV*
g_L	2.32 *nS*	V_{ac}	-25.36 *mV*	S_h	21.96 *mV*
g_T	77.84 *nS*	S_{ac}	15.06 *mV*	h_{min}	0.73
E_T	-79 *mV*	m_{min}	0.37	r	3
I_{com}	0 *pA*	k_{h1}	0.82 *ms/mV*	q_1	1/2
τ_{max}	77.58 *ms*	k_{h2}	1.26 *ms/mV*	q_2	1/2
τ_{min}	6.55 *ms*	b_{h1}	55.86 *ms*		
V_τ	-52.23 *mV*	b_{h2}	282.38 *ms*		

The numerical parameters of the model were obtained from experimental voltage-clamp recordings of the isolated hair cells from the semicircular canal of the rat [5,6] (Table 2).

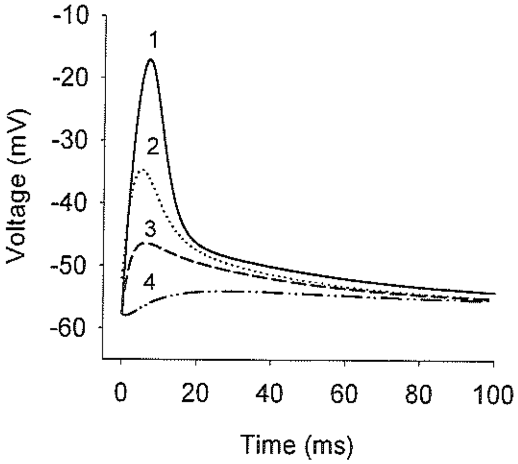

Fig. 3. Voltage response trajectories obtained for $I_{com} = 0$. These traces were obtained for different initial conditions taken for system (1): *(1)* $V_0 = -57.67$ *mV*, $m = 0.0041$, $h_1 = 0.9$, $h_2 = 0.1$; *(2)* $V_0 = -52$ *mV*, $m = 0.240$, $h_1 = 0.8$, $h_2 = 0.2$; *(3)* $V_0 = -57.67$ *mV*, $m = 0.340$, $h_1 = 0.8$, $h_2 = 0.2$; *(4)* $V_0 = -57.67$ *mV*, $m = 0.440$, $h_1 = 0.8$, $h_2 = 0.2$

In figure 3, there are the voltage response trajectories obtained for $I_{com}=0$. The model predicted a resting potential of -57 mV obtained with the values in table 1. The dynamics of the hair cell membrane potential, obtained with the use of the mathematical model shown in (1), qualitatively coincides with the results of the physiological experiments (Fig. 4).

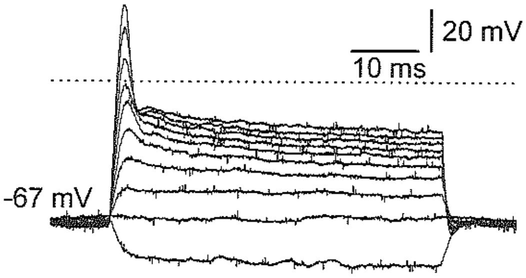

Fig. 4. Traces showing a typical voltage response of a hair cell obtained from the rat's semicircular canals subjected to current pulse injection *(from -0.1 to 0.5 nA) (the dotted line shows the zero voltage)*

2.2 Afferent neuron dynamics

In describing the activity of the primary afferent bipolar neuron, a Hodgkin-Huxley-type model was also used. The parameters were calculated using experimental results obtained from cultured vestibular afferent neurons of the rat [7,8]. The use of rat parameters in this model is the first modification with respect to the original Hodgkin-Huxley model. Other two modifications were about the time constants: an inactivation parameter for outward current "h_K" other is a modification in the mathematical model original of Hodgkin-Huxley where $h + n = 0.8$, here we have next modification $h + n = C(V_2)$, $C(V_2)$ is an experimental results. The right part of this equality has a constant value for each V_2. In addition, our model have a complex description for potassium current $I_K = g_K^{\max} n^4 h_K (V_2 - V_K)$. Based on these modifications and assuming that $\tau_m = 0$ and $\tau_{hk} = constant$ an intersection of two isoclines as an unstable point of repose was found. Therefore, a limit cycle and the correspondent auto-oscillations were also found.

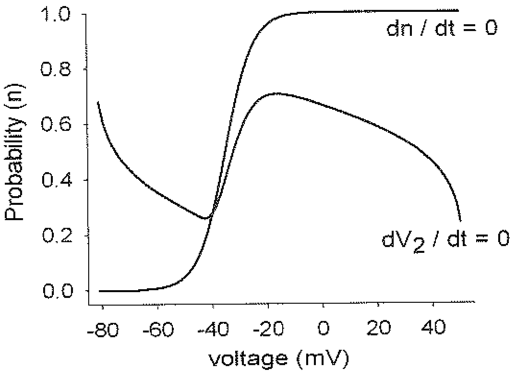

Fig. 5. Isoclines of the simplified and of the modified Hodgkin-Huxley model

The modified and simplified Hodgkin-Huxley model (see above) for the action potential generation takes the form as shown in [4].

$$C_{m2}\frac{dV_2}{dt} = I_{com}(V_1) - g_L^{\max}(V_2 - V_L) - g_{Na}^{\max} m_\infty{}^3(V_2)(C(V_2) - n)(V_2 - V_{Na}) - g_K^{\max} n^4 h_k (V_2 - V_K)$$

$$\tau_n(V_2)\frac{dn}{dt} = n_\infty(V_2) - n \qquad (2)$$

$$\tau_{hk}(V_2)\frac{dh_k}{dt} = h_{k\infty}(V_2) - h_k(V_2)$$

The coefficients $g_{Na}^{\max}$, $g_K^{\max}$, $g_L^{\max}$ belong to confidence intervals in accordance with the experimental results. Table 4 present their values which correspond to the greatest interval between two points (I_1, I_2) of the bifurcation of Hopf [9]. These points indicate the appearance and disappearance of the auto-oscillations.

Table 3. Parameters of the model for vestibular afferent neurons (2)

Activation stable state g_{Na} $m_\infty(V_2) = \frac{1}{1+\exp\left(\frac{-(V_2+33.8)}{5.2}\right)}$	Inactivation stable state g_{Na} $h_{Na_\infty}(V_2) = \frac{1}{1+\exp\left(\frac{V_2+60.5}{9.9}\right)}$
Activation stable state g_K $n_\infty(V_2) = \frac{1}{1+\exp\left(\frac{-(V_2+35)}{5}\right)}$	Inactivation time constant g_{Na} $\tau_{hNa}(V_2) = \frac{1}{0.01+\exp\left(\frac{79+V_2}{-15}\right)+\exp\left(\frac{30+V_2}{5}\right)} + 0.5$
Activation time constant g_K $\tau_n(V_2) = \frac{68}{\exp\left(\frac{25+V_2}{-15}\right)+\exp\left(\frac{30+V_2}{20}\right)}$	Inactivation stable state g_K $h_{K\infty}(V_2) = \frac{0.96408-0.7329}{1+\exp\left(\frac{V_2+33.87968}{10.24986}\right)} + 0.7329$
	Inactivation time constant g_K $\tau_{h_K}(V_2) = \frac{1250}{\exp\left(\frac{15+V_2}{-15}\right)+\exp\left(\frac{25+V_2}{10}\right)} + 500$

Table 4. Numerical parameters of the model (2).

Constants	Units	Chosen Value	Constants	Units	Chosen Value
C_{m2}	μF/cm^2	1	g_{Na}^{max}	mS/cm^2	2.3
V_{Na}	mV	52	g_K^{max}	mS/cm^2	2.4
V_K	mV	-84	g_L^{max}	mS/cm^2	0.03
V_L	mV	-63	I_{com}	μA/cm^2	1 to 150

The amplitude of the auto-oscillations depends on the value of I_{com} (where $I_{com} = -I_{syn}$). The first point of bifurcation $I_1 = 0.6\ \mu A/cm^2$, the second point of bifurcation of Hopf $I_2 = 165.3\ \mu A/cm^2$.

2.3 Synaptic transmission, mechano-electrical transduction and transducer adaptation

Data from experimental studies of synaptic transmission in the bullfrog inner ear [10] were used for the association of the blocks that describe the dynamics of ionic currents in the hair cell and in the primary afferent neuron (Fig 2). The curve shown in figure 6 shows the relationship between the voltage in the hair cell (V_1 in model 1) and the synaptic current in the afferent neuron (I_{syn} equivalent to I_{com}). The maximum synaptic current was hypothesized to be equivalent to 40 μA/cm^2.

Let us add, to the chain of three blocks just described, an input block for the mechano-electrical transduction mechanism [1], and the mechanism of the hair cell transducer adaptation to the prolonged mechanical stimuli. The mathematical model of these two mechanisms is represented in the form of equation (3).

The adaptation mechanism is given by [4]. Where s is the adaptation parameter; τ_{ad} is a time constant; k is a gain constant; I_{Tr} is the transduction current; I_{Tr0} is the transduction current in stationary state; $p(x,s)$ is the probability of the opening of the canal; x is the displacement of a hair bundle.

$$\tau_{ad}\dot{s} + s = k(I_{Tr} - I_{Tro}); \quad I_{Tr} = g_{Tr}(x,s)(V_1 - E_{Tr}); \quad g_{Tr} = \bar{g}_{Tr}\, p(x,s);$$

$$g_{Tr} = 1.4nS; \quad \tau_{ad} = 100\, ms; \quad p(x,s) = \frac{1}{1 + Exp\left(-\frac{x+s-x_0}{s_1}\right)}; \qquad (3)$$

$$s_1 = 0.2\,\mu m; \quad k = 0.03; \quad \mathrm{I_{Tr0}} = -14.4\,\mathrm{pA}; \quad x_0 = 0.3\,\mu m; \quad E_{Tr} = 0$$

Using this system, a mathematical model of the vestibular mechanoreceptor information output was obtained. It consists of equations (1), (2), (3), tables 1, 2, 3, 4 and the graph in Figure 6.

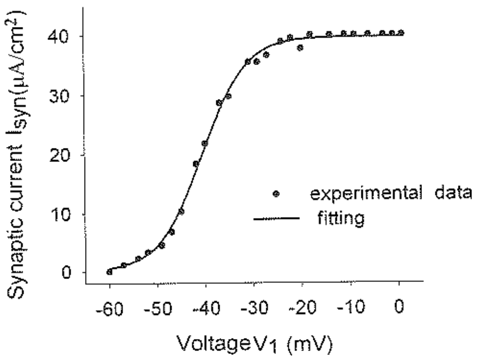

Fig. 6. Relationship between the membrane voltage in the hair cell and the synaptic current in the afferent neuron. Continuous line represent the best fit to the experimental data [10].

3 Numerical Results

After the association of all blocks of the model and the analysis of the dynamics of ion currents in the hair cell and in primary afferent neuron, the numerical parameters were selected on the basis of physiological experiments (tables 1, 2, 3 and 4). The results of the calculations for the initial stage of the fall are shown in Fig 7 (the inclination forward to 30 degrees-Figure 7A-). Development of membrane potential V_1 of hair cell as a result of the mechanism of adaptation acting against the background of the mechanical stimulus are shown in Figure 7 B. Finally we have a secondary information in the form of afferent impulses of the primary neuron with frequencies varying from 20 Hz to 40 Hz.

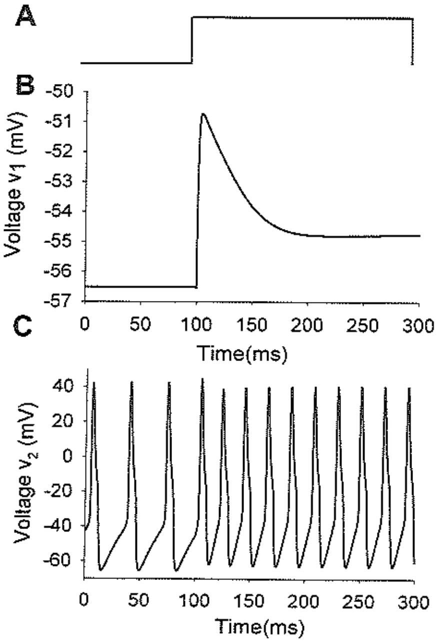

Fig. 7. The process of the information output from the vestibular mechanoreceptor. In *A*, mechanical stimulus displaces a hair cell bundle. Stimulus is absent during the first *100 ms* (stationary situation of rest); in the course of the following *200 ms* the hair bundle is displaced 1 μm. In B, the voltage response of the hair cell reflects the activation of the transducer adaptation mechanism. In C, the output of the model in the form of action potentials in the primary afferent neuron.

4 Conclusion

The numerical results indicate that the mathematical model of information processing in the gravito-inertial mechanoreceptor resembles the activity of the natural sensor as studied experimentally.

In the development of vestibular prosthetic devices a transfer function derived from the recordings in the monkey inner ear [11] has been used to convert the analog output of the device to a pulse train useful to stimulate the afferent nerve. We propose that the use of more realistic models based on the physiological knowledge and using parameters from animal experiments, will endow prosthetic devices with greater coding capabilities than those of devices using simpler transfer functions.

Our results demonstrate that the development of an integrated mathematical model of the function of vestibular endorgans is feasible and that it will resemble vestibular system coding capabilities.

It is concluded that the proposed mathematical model may be used to construct an encoder system for artificial sensors (eg: microaccelerometer and microgyroscope) contributing to the development of a reliable vestibular prosthesis prototype.

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