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ORIGINAL PAPER

Macrophage ion currents are fit by a fractional model and therefore are a time series with memory

Darío Manuel Domínguez · Mariela Marín · Marcela Camacho

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Abstract We studied macroscopic ion currents from macrophages and compared their patterns of behavior using classical and fractal analysis. Peak and steady state currents were measured respectively at the beginning and end of a voltage-clamp pulse. Hurst coefficients H and fractional dimensions were calculated for the current fluctuations (I_H) during the intervening interval; these fluctuations are usually assumed to be white noise. We show that I_H is different from 0.5 and that the increments are stationary, indicating that the dynamic model has memory and that the intervening current fluctuations cannot be considered as white noise. I_H is less than 0.5, implying an antipersistent pattern. In addition, we show that the relation between inactivation and I_H versus voltage V fit an equation $I_H(V) = f(V, \alpha, m, d)$, where α is associated with fractional calculus and m and d are free parameters. Fitting by a fractional model confirms that the phenomenon has memory.

Keywords Fractal · Macrophage · Ion current · Fractional · Memory

D. M. Domínguez · M. Marín
Facultad de Ciencias, Universidad Militar Nueva Granada, Carrera 11 No. 101-80, Bogotá, Colombia

M. Marín · M. Camacho
Laboratorio de Biofísica, Centro Internacional de Física, AA 49480 Bogotá, Colombia

M. Camacho (✉)
Departamento de Biología, Facultad de Ciencias, Universidad Nacional de Colombia, Sede Bogotá, AA 14490 Bogotá, Colombia
e-mail: mmcamachon@unal.edu.co

Introduction

Biological cell membranes of animals are lipid bilayers, composed of phospholipids and other polar lipids as well as cholesterol, and in which proteins are immersed. Their most obvious function is compartmentalization, and the biggest compartment is that formed by the external membrane of the cell, named the plasmatic or cellular membrane, that separates two solutions with different ion concentrations. The external cellular solution has higher Na^+ and Cl^- concentrations, whereas the internal is rich in K^+ and non-diffusible anions. The cellular membrane functions as a selective permeability barrier and exchanges ions across itself using specialized proteins known as ion channels. Ion channels have internal aqueous pores and are the most efficient proteins for diffusing ions in the direction of their electrochemical potential. Ion channels are ubiquitous in cells; they gate their aqueous pores in response to voltage differences, to ligands or to mechanical stimuli, and are involved in functions related to electrical signals in neurons, muscle contraction and cell signaling.

The cellular membrane as lipid bilayer resembles an electric capacitor, and therefore charges and discharges when an electrical stimulus is imposed. On the other hand, ion channels move charges and therefore behave as conductors. Electrophysiological techniques allow detection of capacitive currents, currents passing through ion channels and cellular membrane potentials, and are used for functional characterization of electrical properties of cellular membrane and ion channels. There are two basic ways to record currents from the cellular membrane with electrophysiological techniques. Single channel recordings are made on only a small patch of the membrane and measure the current through one or few channels. Whole cell recordings are made on the entire cellular membrane, and

macroscopic currents through many ion channels are observed.

Electrophysiological recordings can be studied by two types of analysis. The first type, classical analysis, assumes that the observed phenomenon (the ion current) is random and has no memory of past events. The opening and closing (gating) of an individual ion channel has been considered spontaneous, and the presence or absence of ion current is the functional expression of these fluctuations (Hille 1992). In single channel recordings, the fluctuating state of ion channels is explained by postulating a number of substates, with a channel switching between substates in a random manner with constant probability. A switch between substates therefore depends only on the present substate and not on how long the channel has been in that substate, nor on the history of previous substates (Colquhoun and Hawkes 1985). In whole cell recordings, the classical analysis constructs current–voltage (*I–V*) relations during activation or stationary states of the current, allowing determination of activation and inactivation current parameters. The phenomenon described in the *I–V* relations can be fit by Boltzmann models where the probability is equal for each substate of the channel.

The second type of analysis, fractal analysis, assumes that the single channel current is a phenomenon that has memory. That is, single ion channel fluctuations can be treated as arising from movement through a large number of substates, where switching between substates may vary in time. Switching between substates may be linked, and therefore previous states are important (Bassingthwaighte et al. 1994). This type of analysis predicts that the apparent duration of the channel open and close times will vary inversely against the scale of the time series observed. Therefore short time series reveal brief openings or closings whereas long time series reveal long openings and closings (Liebovitch and Sullivan 1987; Liebovitch et al. 1987; Mandelbrot 1983).

Classical and fractal analysis have been applied to single channel recordings, particularly on experimental data from excitatory cellular membranes such as those found in neurons. Much less work has been done in other models. In this work, we studied macroscopic ion currents through cellular membranes from cells of the immune system, using the whole cell configuration of the patch clamp technique (Hamill et al. 1981). Classical analysis showed inactivation versus voltage relationships similar to those previously reported. The results obtained with fractal analysis, which generally assumes that a time series can be rescaled by arbitrary ranges, show that I_H, a measure of the fluctuations of the current, differs from 0.5, meaning that the current as a time series cannot be regarded as white noise. Moreover, the I_H calculated are less than 0.5, indicating an antipersistent behavior, and the relation I_H versus voltage can be fit by a fractional model, further supporting the idea that this constitutes a phenomenon with memory.

Experimental

Cell culture

The murine macrophage-like cell line J774.A1 was obtained from the European Cell line and Hybridoma Bank Collection (ECACC, the European Human Cell Bank and the Hybridoma Collection No. 91051511, Porton Down, Salisbury, Wiltshire, UK) and maintained as a monolayer in 25 cm^2 flasks at 37°C with 5% CO_2 for up to 4 weeks. Cells were kept in RPMI 1640 culture medium (Sigma-Aldrich Corp., St. Louis, MO, USA) supplemented with 10% fetal bovine serum (Hyclone, Logan, UT, USA). Suspended cells were allowed to attach onto sterile glass coverslips kept in 35 mm Petri dishes at 37°C for 24 h prior to electrophysiological studies. The medium was changed daily and one hour before recording.

Electrophysiological recording

Coverslips were placed in a recording chamber kept at room temperature (18°C) on the stage of an inverted Zeiss IM35 microscope (Zeiss, Germany). Cells were bathed in a solution consisting of (in mM) 145 NaCl, 5 KCl, 1 $CaCl_2$, 2 $MgCl_2$, 10 HEPES-Na, 5 glucose at pH 7.34 and 300 mOsm. Macroscopic currents were recorded in the whole cell configuration of the patch-clamp technique with an Axopatch-1C amplifier (Molecular Devices, Sunnyvale, CA, USA). Pipettes were pulled from non-heparinized hematocrit capillaries and had resistances of 2.5–5 MΩ when filled with a solution containing (in mM): 140 K glutamate, 2 KCl, 5 EGTA·K, 0.5 $CaCl_2$, 4 $MgCl_2$, 10 HEPES·K, 3 ATP·Na_2, 0.5 GTP·Na at pH 7.34 and 300 mOsm. During whole cell recording, the series resistance was not greater than 10 MΩ and was left uncompensated. The cell was maintained under voltage-clamp throughout the experiment. Voltage steps were applied from a holding potential of −60 mV. Data were sampled at 5 kHz, filtered at 1 kHz and digitized at 200 μs/point with a Digidata 1200 interface (Molecular Devices, Sunnyvale, CA, USA). Data acquisition and analysis were performed with pCLAMP 6 (Molecular Devices, Sunnyvale, CA, USA) and plotted with Origin 7 (OriginLab Corp., Northampton, MA, USA).

Data analysis

Recordings were converted to Microsoft Excel 4.0 and then transferred to Benoit 1.1 fractal analysis software (TruSoft International, St. Petersburg, FL, USA). Peak current (I_p) was taken as the maximal current after the capacitive transient, and the stationary current (I_{ss}) as the mean current at the end of the pulse between 299 and 337 ms for the

inward rectifying potassium current and between 790 and 830 ms for outward currents. *H* was calculated from the Rescaled Range test *R/S* (Bassingthwaighte et al. 1994) using the Benoit software. In fractal analysis, time series can be rescaled by arbitrary ranges. In the Rescaled Range test *R/S*, the Range *R* is the difference between the maximum and minimum of the deviation from the mean of the running sum of the data, normalized by the standard deviation *S*; for each *R/S* range (t, t') estimated from a log–log regression *R/S* versus t' the time interval length, the slope is the Hurst coefficient (*H*) of the time series. Low *H* values indicate a high degree of roughness. The fractal dimension D_f was calculated by equation

$$D_f = 2 - H \quad (1)$$

Results

Macroscopic currents from macrophages

Macrophages are cells that participate in the immune response and are involved in phagocytosis and antigen presentation. Several macroscopic currents have been described in macrophages (Gallin 1991). Among these currents, two are prominent: an inward rectifying potassium current (I_{Kir}) and an outward current with partial inactivation (I_{Out}; Gallin and Sheehy 1985; McKinney and Gallin 1988; Randriamampita and Trautmann 1987) that appear to be the result of activation of Kir2.1, Kv1.3 and Kv1.5 ion channels (Vicente et al. 2003; Park et al. 2006; Vicente et al. 2006). The macroscopic currents recorded are composed of many current events arising from the ion channels present in the macrophage cellular membrane. In order to characterize the kinetics of macroscopic current recorded by a glass electrode, the cellular membrane potential was changed over a period of time and returned to a holding potential, and the elicited current recorded (Fig. 1a). Typical macroscopic I_{Kir} and I_{Out} recordings from macrophages are shown in Fig. 1b and c. I_{Kir} is characterized by an inward current carried by potassium, which activates quickly and inactivates over time at very hyperpolarized (negative) pulses. This current is probably

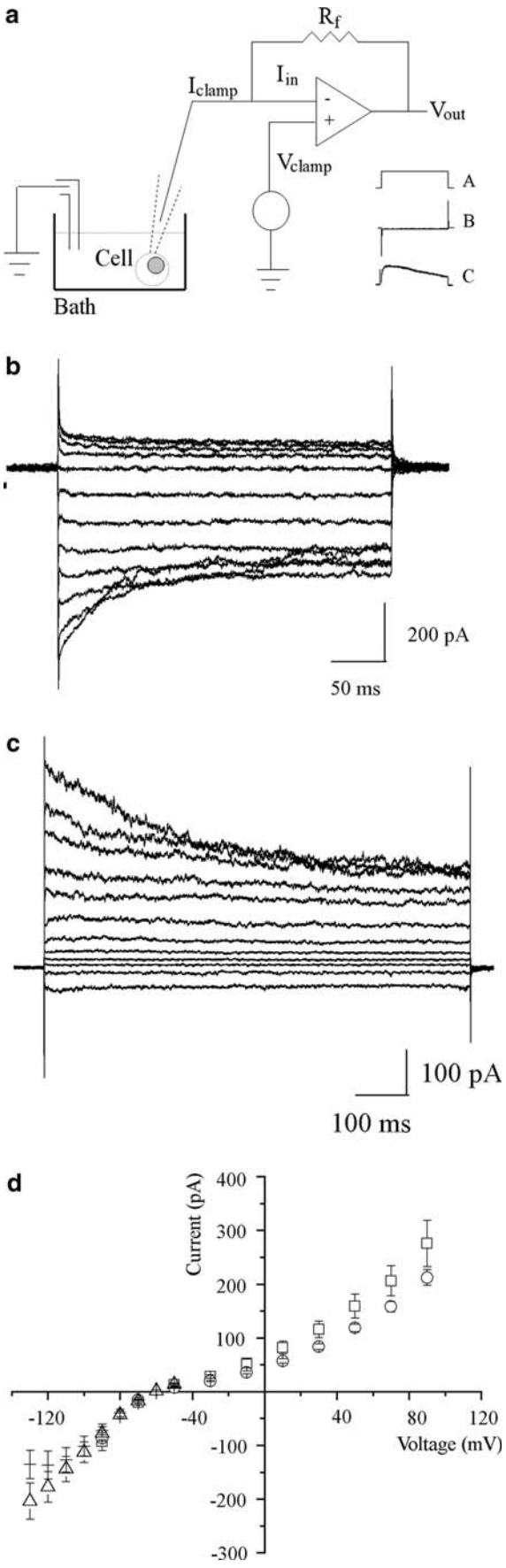

Fig. 1 Macroscopic currents of macrophages and their *I–V* relations. ▶ **a** Macroscopic currents were recorded with a setup as shown; *A* represents a pulse of ΔV imposed onto the cellular membrane; *B* the resulting capacitive transient; and *C*, the resulting macroscopic current. **b** A representative I_{Kir} elicited in response to voltage steps of 300 s from a holding potential of −60 mV. Nine voltage steps were imposed onto the cellular membrane, from −130 to −40 mV, every 15 s, with 10 mV increments between steps. **c** A representative I_{Out} elicited from the same holding potential with 9 voltage steps of 1 s, every 15 s, from −70 to 90 m, with 20 mV increments. **d** *I–V* relationships for recordings in **b** and **c**. (Δ) I_{Kir} I_p, (+) I_{Kir} I_{ss}, $n = 11$; I_{Out} I_p and (O) I_{Out} I_{ss}, $n = 22$. Data represent mean ± SE

the result of only one type of channel, Kir2.1, and is blocked by Ba^{2+} (Gallin 1991). I_{Out} is carried partly by potassium (data not shown), is characterized by a fast activation and partial inactivation, and appears to be the result of more than one type of channel (Gallin 1991). In this study we compare these macroscopic currents using the two types of analysis described above: classical (Colquhoun and Hawkes 1985) and fractal (Glockle and Nonnenmacher 1995; Liebovitch 1996).

Classical analysis of macrophage macroscopic currents

The apparent current peak (I_p) and the current at the end of the pulse (I_{ss}) were calculated and plotted against membrane potential as shown in Fig. 1d. The signal in the interval between the times to I_p and I_{ss} is assumed to be white noise and is not further analyzed in the classical analysis. The peak I_{Kir} was measured 42 ms after the initiation of the voltage step, when the capacitive transient was clearly over. The I_p of I_{Kir} at −130 mV was −203 ± 33.5 pA ($n = 11$) and the mean I_{ss} at the end of the pulse was −135 ± 26.4 pA. The ratio I_{ss}/I_p was used as an estimate of the degree of inactivation of I_{Kir}. Partial inactivation occurs at negative voltages to −90 mV, and the inactivating components of I_{Kir} increase at the most negative voltage studied. The potential at which I_{Kir} conductance is 50% of its peak value was −88 mV. I_{Kir} can be fit by Boltzmann models (Forero et al. 1999).

The peak I_{Out} was measured at least 40 ms after the voltage step. I_{Out} activates at potentials greater than −10 mV. The I_p of I_{Out} at 90 mV was 275 ± 43 pA and the I_{ss} (mean current at the end of the pulse) was 212 ± 14.7 pA. I_{Out} inactivated by 23 ± 3.7%. The I_{ss}/I_p ratio was plotted versus voltage for I_{Kir} ($n = 11$ cells) and I_{Out} ($n = 22$ cells), as shown in Fig. 2a and b. I_{Out} was not well fit by Boltzmann models or other similar approaches, motivating the further analysis of this current using fractal analysis.

Fractal analysis of macrophage macroscopic currents

Calculation of D_f as well as of I_H by rescaled range analysis was performed in the current interval between times to I_p and I_{ss}, where signals are usually assumed to be white noise (42–290 ms for I_{Kir} and 42–790 ms for I_{Out}), corresponding to a non-stationary process. In other words, if current is denoted as $I_H(t)$, $I_H\ (t + \Delta t) - I_H(t)$ depends only on Δt. For I_{Kir} and I_{Out} recordings, the calculated $I_H(t)$ were different from 0.5, below this value and with stationary increments of Δt (as seen in Fig. 1b and c, for maximum ΔVm). These results indicate that the current fluctuations during the period of time studied are not white noise but are negatively correlated. The I_{Kir}

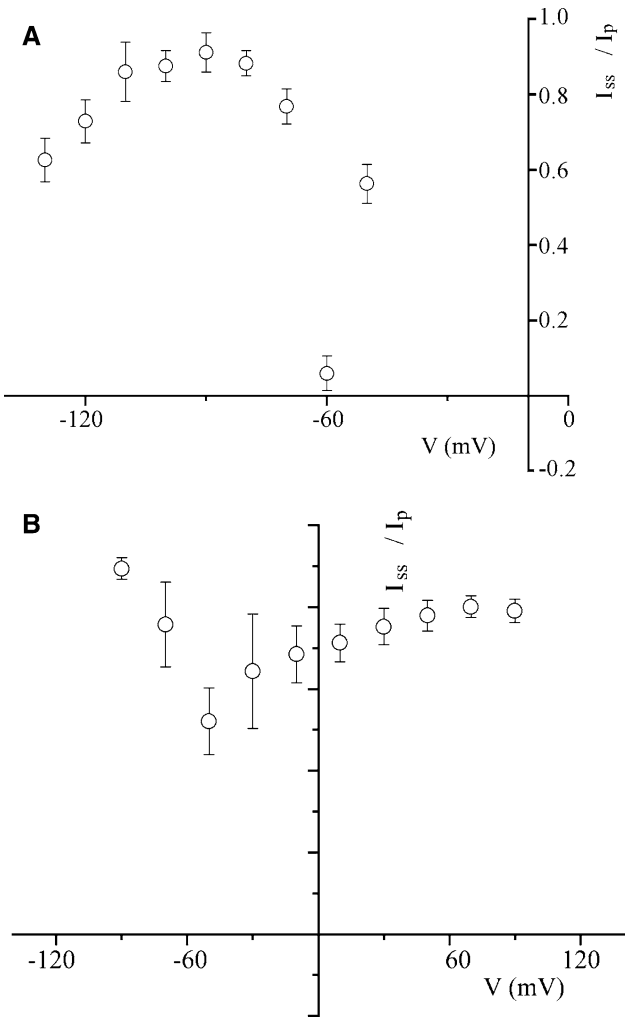

Fig. 2 Inactivation curves of macroscopic currents of macrophages. Mean current at the end of the pulse/peak current (I_{ss}/I_p) versus voltage. **a** Mean I_{ss}/I_p I_{Kir}, **b** Mean I_{ss}/I_p for I_{Out}. Data represent mean ± SE

and I_{Out} recordings (Fig. 1a and b) show fluctuations that appear to be self-similar. $I_H(t)$ was plotted against voltage (see Fig. 3a and b); the relation has the same pattern as in plots of the ratio I_{ss}/I_p versus voltage for I_{Out} (Fig. 2b).

Current fluctuation ($I_H(t)$) as a function of voltage is fit by a fractional model

A value of $I_H(t)$ different from 0.5 and stationary increments of Δt indicate a process with memory (Fig. 3a and b). Upon a voltage stimulus, $I_H(t)$ indicates memory and antipersistence. Despite that the initial conditions were always the same previous to a ΔVm, $I_H(t)$ also varied. The relations obtained were therefore fit with models that also have memory such as those derived from fractional calculus (Carpentieri and Mainardi 1997; Glockle and

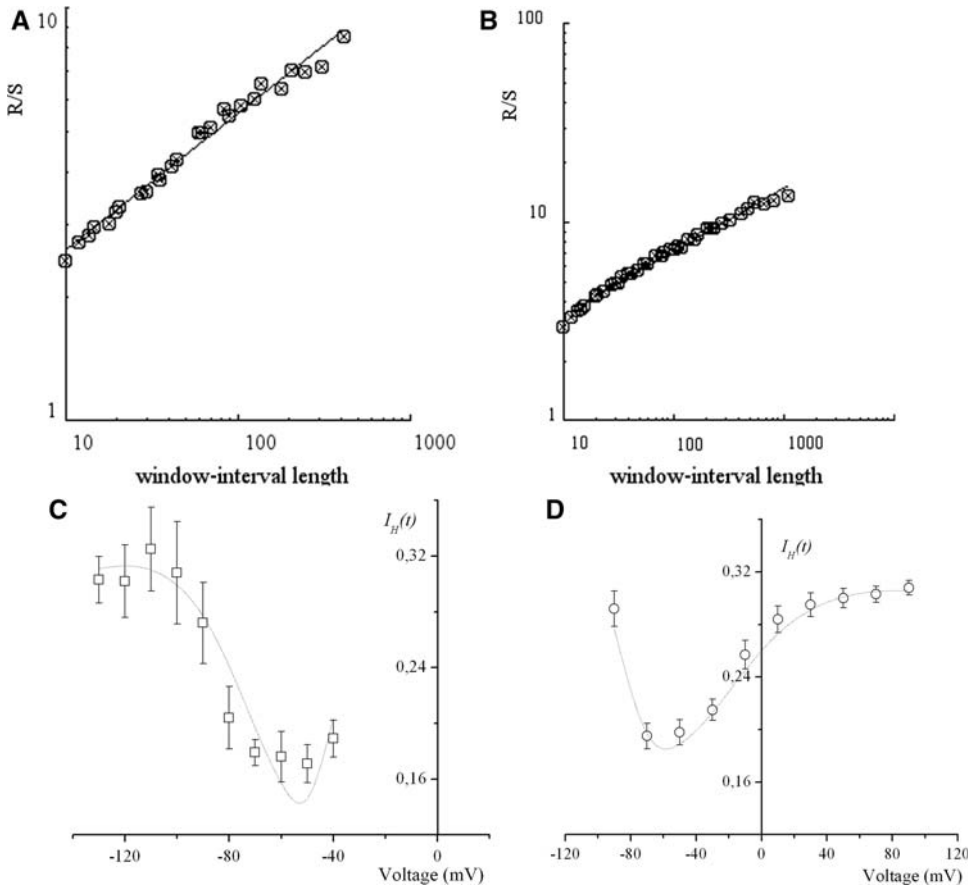

Fig. 3 Hurst coefficient versus voltage curves from macroscopic currents of macrophages. **a** R/S versus time curve for I_{Kir} and **b** for I_{Out}. **c** Mean $I_H(t)$ for I_{Kir} and **d** mean $I_H(t)$ for I_{Out}. Data represent mean ± SE. *Dotted lines* represent fitting curves obtained with Eq. 2

Nonnenmacher 1995; Liebovitch 1996; Metzler and Klafter 2004; Picozzi and West 2002; Vargas et al. 2003a, b). The model with the best fit is given by the following equation:

$$I_H(t)(V) = \frac{2}{\alpha} e^{(\mathrm{mV}+d)\cos\left(\frac{\pi}{\alpha}\right)} \cos\left((\mathrm{mV}+d)\sin\left(\frac{\pi}{\alpha}\right)\right) + 0.28 \quad (2)$$

This fractional equation fits $I_H(t)$ as a function of voltage V for both I_{Kir} and I_{Out} (Fig. 3a and b). The fits are significant by χ^2 analysis ($P < 0.01$). The parameters m and d in this equation are scaling parameters, and α is the order of the differential equation. For $I_{Kir,}$ at voltages between −130 and −40 mV, the values found were $m = 0.031$, $d = 0$, and $\alpha = 1.40$. For $I_{Out,}$ at voltages between −90 and 90 mV, the values found were $m = 0.031$, $d = 5.05$, and $\alpha = 1.35$. The fits for I_{Out} were better than that for I_{Kir}. The $I_H(t)$–voltage relation is a restricted function of the solution to the fractional differential equation:

$$D^{(\alpha)}I(v) - \frac{v^{-\alpha}}{\Gamma(1-\alpha)} = -I(v) \quad (3)$$

The solution to this equation is of the Mittag–Leffler form, $E_\alpha(-v^\alpha) = I(v)$, in which $I(v)$ can be written as:

$$I(v) = B_\alpha(v) + I_H(v) \quad (4)$$

When $H < 0.5$, one has $\alpha = 2/(2H_0 + 1)$ (Darses and Saussereau 2007). The first of the two summands can be written as

$$B_\alpha(v) = \int_0^\infty K_\alpha(r) e^{(-k(r)v)} dr \quad (5)$$

where $K_\alpha(E)$ represents a distribution of energy barriers of the form

$$K_\alpha(r) = \frac{1}{\pi} \frac{r^{\alpha-1}\sin(\pi\alpha)}{r^{2\alpha} + 2r^\alpha \cos(\pi\alpha) + 1} \quad (6)$$

The remaining summand can be written as

$$I_H(v) = \frac{2}{\alpha} e^{(v\cos(\pi/\alpha))} \cos(v\sin(\pi/\alpha)) \quad (7)$$

Note that this function has the same value for the period of oscillation as the exponential decay constant. From $v = \mathrm{mV} + d$, Eq. 2 is obtained, which fits the data for $I_H(V)$. Therefore $B(V)$ provides information about energy or energy barriers and the integral (Eq. 5) about the energy spectra, while Eq. 2 derived from Eq. 7, fits the fluctuations of the current recorded by whole cell. Finally, the asymptotic representation of the solution provides information as to the function of the memory in the model

$$I(v) \approx \frac{v^{-\alpha}}{\Gamma(1-\alpha)} = \frac{1}{v^{\alpha}} \frac{1}{\Gamma(1-\alpha)} = c\left(\frac{1}{v}\right)^{\alpha} \quad (8)$$

The α values found for I_{Kir} and $I_{Out,}$ 1.40 and 1.35, respectively, can be expressed as $I_H(t)$ values using $\alpha = 2/(2H_0 + 1)$ (Darses and Saussereau 2007) when $H < 0.5$, then the H_0 value for I_{Kir} and I_{Out} are 0.214 and 0.24, respectively.

Discussion

The study of the macroscopic currents I_{Kir} and I_{Out} of macrophages was performed with classical and fractal analysis. The classical analysis reproduces published data for these cells. Current expression, density and activation and inactivation kinetics are as have been previously described (Gallin 1991; Forero et al. 1999). I_{Kir} can be fit by Boltzmann models (Forero et al. 1999) but I_{Out} was not fit satisfactorily with such models. Therefore the observed behavior of this type of current requires going beyond the classical analysis.

In fractal analysis, the use of short length time series has been argued to be unreliable (Hoop and Peng 2000). Our study was done on 1,200 events for I_{Kir} and 3,800 events for I_{Out}. In terms of the amount of data and the length of time analyzed, these series could be therefore considered long. The current fluctuation over time studied included the interval considered white noise, for which $I_H = 0.5$ is expected. The results presented here show that I_H differs from 0.5 for either macroscopic current, indicating that the time series is not white noise, has fractal characteristics and could be referred to as fractal noise.

I_H between 0.5 and 1 correlate positively with the fluctuations and are known as persistent; I_H between 0 and 0.5 correlate negatively with the fluctuations and are known as antipersistent, as is the case for I_{Kir} and I_{Out}. Long time series of membrane voltage fluctuations in T-cells have been found to be antipersistent, and it has been suggested that increases of membrane voltage are more likely to be followed by decreases of membrane voltage (Churilla et al. 1996). In single channel gating studies, antipersistency suggests that if the channel is in an open state it will be followed by a closed state. For the macrophage currents shown here, the antipersistent pattern may indicate that presence of macroscopic currents is likely followed by decrease or absence of the current. It appears desirable to have this type of pattern in a cellular membrane, because persistent currents will dissipate the electrochemical gradients over time. Most cellular membranes spend nearly 2/3 of their chemical energy pumping ions against their gradients because nutrients transport and cell signaling depend on the energy store in these gradients. We would like to speculate that in addition to pumping of ions by ion pumps, autoregulation of ion channels by closing warranty the maintenance of electrochemical gradients and conditions far form equilibrium required for normal cell functioning.

The I_{Kir} and I_{Out} current recordings present a fractal pattern with $I_H < 0.5$ (negative correlation), stationary increments of Δt in a non stationary process, and with $I_H(t)$ versus voltage relations well fit by a fractional equation. The behavior of both macroscopic currents therefore appears to represent a phenomenon with memory (Bassler et al. 2006). Our experimental data are fit by an equation that is one of the summands of Mittag–Leffler solution described in terms of voltage.

In enzymes, single molecule analysis has shown that the enzyme activity is also a phenomenon with memory (Flomenbom et al. 2005; English et al. 2006). In the case of lipase, enzyme activity measured by the waiting time probability density function of the off state and the state correlation function fit stretched exponentials showing non-exponential behavior of these biomolecules (Flomenbom et al. 2005). For β-galactosidase, enzyme activity reveals a memory phenomenon. From functional data these authors suggest that enzyme activity arrives from many conformational substates and the correlations found also suggest a phenomenon with memory.

The physical significance of the observed phenomenon relates to a response in terms of stress–strain (viscoelastic model), during activation, inactivation and stationary state in which there is a current response to a voltage step stimuli, where time is kept constant The Hurst calculated indicates that the phenomenon is not random (Bassler et al. 2006), suggesting memory but the current elicited by a voltage step follows a model of decays and oscillation that its fit by a fractional differential equation confirming memory.

The biological significance for ion currents showing fractal behavior may be related to the fact that fractal processes are more tolerant to error (Hoop and Peng 2000) and may autoregulate. Macroscopic currents also reflect the behavior of the ion channel population. Populations of channels in which single channel behavior is relatively homogeneous appear be easy understood by classical analysis and fit by Boltzmann models (i.e. I_{Kir}). However when single channel behavior differs significantly between individual molecules the macroscopic pattern may require further analysis as the one shown here (i.e. I_{Out}).

The fractional model found has an exponential component that implies decay, and a harmonic component that implies oscillation. The fractional model also includes an α value. Values of $0 < \alpha < 1$ are related to relaxation phenomena, and values of $1 < \alpha < 2$, to oscillatory phenomena (Carpentieri and Mainardi 1997). Flomenbom

et al. (2005) show relaxation phenomena of enzyme activity obtaining α values lower than 1. In this study we show oscillatory phenomena whit α values between 1 and 2 (Carpentieri and Mainardi 1997). Other authors relate this α value to normal diffusion ($\alpha = 1$), anomalous diffusion ($\alpha \neq 1$), and turbulence ($\alpha > 2$; Goychuk and Hanggi 2004; Metzler and Klafter 2004).

I_{Kir} is believed to set the macrophage cellular membrane potential (Gallin 1991) and is altered by *Leishmania* infection (Forero et al. 1999). Alterations of I_{Out} have been associated with activation (Buchmuller-Rouiller and Mauel 1991; Fisher et al. 1995; Ilschner et al. 1996; McKinney and Gallin 1992; Vicente et al. 2003; Camacho et al. 2008), differentiation and replication (DeCoursey et al. 1996; Ilschner et al. 1996), oxygen radical production (Holevinsky and Nelson 1995), phagocytosis (Berger et al. 1993), and indicates readiness for antigen presentation (McKinney and Gallin 1992); all of these are typical macrophage cellular responses. I_{Kir} is probably the result of events arising from a population of identical ion channels, whereas it has been suggested that I_{Out} may be the result of a population of more than one type of ion channels (Gallin 1991). Moreover, our data also indicate that parameters such as dwell time, obtained from single channel recordings, could be calculated from whole cell recordings.

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