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# Dependence of firing pattern on intrinsic ionic conductances: Sensitive and insensitive combinations

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**Abstract**

We construct maps of the intrinsic firing state (silent, tonically firing, or bursting) of a model neuron as a function of its maximal ionic conductances. The firing properties vary significantly only in response to changes in particular, sensitive combinations of conductances that may serve as targets for neuromodulation. Less sensitive combinations define directions along which neuronal conductances may drift without triggering significant changes in firing activity. This suggests that neurons may have similar functional properties despite widely varying conductance densities. 

*Keywords:* Conductance-based model; Activity-dependent regulation; Neuromodulation; Stomatogastric ganglion

## 1. Introduction

Electrophysiological measurements of ionic conductances show significant cell-to-cell variability [1,3]. Although traditionally attributed to artifacts of the recordings, we have shown that this variability may be a natural feature of how neurons are built [1], conferring onto them stability of activity while allowing for conductance variability resulting from turnover of channel proteins and their regulation. We have also shown that variability of the maximal conductances in a conductance-based model neuron does not necessarily imply variability in its activity patterns (Golowasch et al.,

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unpublished observations). Broad areas in a multidimensional parameter space define characteristic activity patterns, with activity specified by several conductances rather than by single conductances alone.

In the present article we examine in more detail the contribution that each conductance makes to activity, both across activity pattern boundaries and, more specifically, within the regions of parameter space for each type of activity.

## 2. Methods

A conductance-based model was built using standard Hodgkin–Huxley equations to describe each one of five voltage-dependent conductances ($I_{Na}$, $I_{Kd}$, $I_{Ca}$, $I_{KCa}$, and $I_A$) and a leak current. Currents were based on measurements in the stomatogastric ganglion (STG) [5] and can be found in [3]. We fixed the maximum conductance corresponding to each of the currents at various different values and identified the resulting patterns of activity as either silent, tonic action potential firing, or bursting. Cells with constant membrane potentials were classified as silent. Cells with clusters of action potentials separated from each other by long silent intervals were classified as bursters. Cells with regular action potential firing were classified as tonically firing cells or as single-spike bursters, depending on their ability to cause transmission at a model synapse based on measurements of graded synaptic transmission within the STG [4].

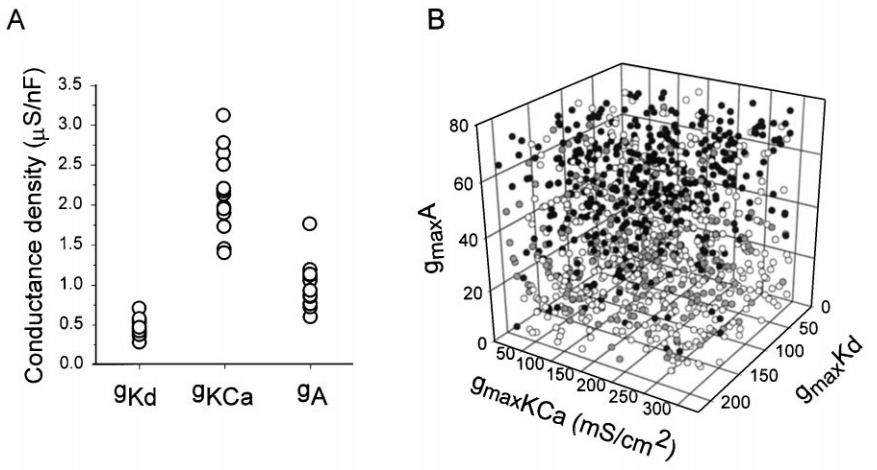


Fig. 1. Variation in conductance densities in the crab PD neuron and in the model neuron. (A) Measurement of the three outward conductances in 13 different PD neurons. Conductance densities vary over a factor of 2.5 for $g_{Kd}$, 2.2 for $g_{KCa}$, and 3.0 for $g_A$. (B) Firing state of the model neuron as a function of the three outward currents' maximal conductances. $g_{max}Ca$ and $g_{max}Na$ were varied randomly. The firing state cannot be determined by specification of only the maximal conductances of the three outward currents. Intrinsically silent (black points), tonically firing (gray points), and bursting (white points) activity patterns each fill the entire region of parameter space over which these three conductances were varied.

We measured the peak conductances of the three $K^+$ currents ($I_{Kd}$, $I_{KCa}$, and $I_A$) expressed by isolated pyloric dilator (PD) neurons of the stomatogastric ganglion of the crab *Cancer borealis* in voltage clamp ([1], Fig. 1). Conductance densities were calculated by normalizing the peak conductances against the capacitance of the cell, which was measured by integrating the capacitive current during a brief voltage clamp test pulse [1].

## 3. Results

Fig. 1 illustrates the complexity of the parameter space for the three outward conductances measured in real PD neurons (Fig. 1A), and for the same three conductances in the model neuron (Fig. 1B). Although PD cells possess a characteristic pattern of activity, the outward currents show a large degree of variability in their peak conductances (Fig. 1A). This suggests that these currents can vary within very wide margins without disrupting activity. The wide variability in individual conductances also suggests that measurement of a single conductance is not sufficient to determine the cell's activity state. We therefore tested whether measurement of single conductances, or even all three outward currents, was sufficient to characterize the intrinsic firing state of the model neuron (Fig. 1B). We found that, while some trends existed, the measurement of the three outward conductances was insufficient to specify the intrinsic firing state (silent, tonic, or bursting). Each one of the three patterns of activity occupies the whole three-dimensional parameter space. Thus, no combination of outward currents determines uniquely a state of activity, and each activity pattern is highly permissive of variations in maximal conductance of the outward currents in the cell.

In contrast, when another combination of conductances is examined (something that can only be done with a model cell), we find that the parameter space appears clearly structured (Fig. 2A). Regions with different patterns of activity are reasonably well separated, though each state of activity is defined broadly by these parameters, and we observe slabs of parameter space occupied by each activity pattern. The maximal conductances shown, $g_{\max}Ca$, $g_{\max}A$, and $g_{\max}Kd$, are found to be the most important conductances in separating the tonic region of activity from the bursting region. That is, changes in a combination of these three conductances that point across the border between the tonic and bursting regions would be most effective in changing activity from tonic to bursting. In contrast, changes along directions that do not cross regional boundaries, or changes in conductances to which the neuron's activity pattern is not sensitive, could be quite large without producing a significant modification in activity. For example, changing $g_{\max}KCa$ did not strongly affect the cell's activity, while replacing $g_{\max}Kd$ in the plot by $g_{\max}Na$ led to a slightly better separation of the tonic points from the silent points (Goldman et al., unpublished observations).

We next looked at details within each of the regions in parameter space (Fig. 2B–D). This allowed us to test whether the firing properties within the firing regions were sensitive to the same conductances that were important in distinguishing

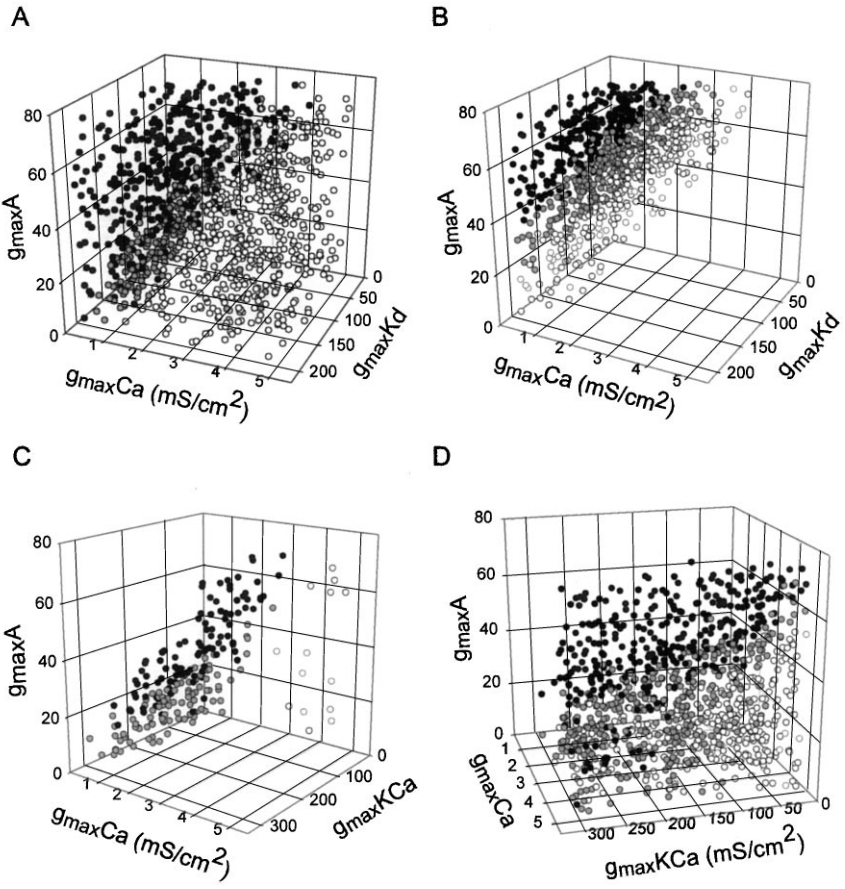


Fig. 2. Dependence of the model neuron's activity patterns on its underlying maximal conductance densities. (A) Specification of $g_{\max}A$, $g_{\max}Ca$, and $g_{\max}Kd$ leads to a strong separation of the firing states into particular regions of the parameter space. Shading is as in Fig. 1B. (B) Steady-state voltage levels for the intrinsically silent cells. (Black) $-54.8$ to $-53.0$ mV; (gray) $-53.0$ to $-51.7$ mV; (white) $-51.7$ to $-45.5$ mV. (C) Action potential firing rate for tonically firing cells. (Black) 0.35 to 1.10 Hz; (gray) 1.15 to 2.50 Hz; (white) 24.0 to 89.6 Hz. (D) Bursting rate for bursting cells. (Black) 0.2 to 1.04 Hz; (gray) 1.05 to 1.14 Hz; (white) 1.15 to 2.40 Hz.

between regions. We separated the silent cells into groups with different levels of depolarization (Fig. 2B) and looked for sets of three conductances that revealed a clear separation of the different levels. We found that the combination of $g_{\max}A$, $g_{\max}Ca$, and $g_{\max}Kd$ best defines the steady-state level of depolarization of silent cells, while other combinations are significantly less adequate. The tonic region was next characterized by identifying the action potential firing rate of the different cells (Fig. 2C), and the best separation was obtained by a combination of $g_{\max}A$, $g_{\max}Ca$, and $g_{\max}KCa$. The KCa conductance had little effect in separating the low (black) and middle (gray)

firing rate cells. However, the high firing rate neurons are all characterized by values of $g_{\max}KCa$ that are very close to zero. Inspection of the voltage traces of these cells shows that their firing is not a 'classic' tonic firing, but rather is characterized by a depolarized baseline membrane potential similar to the baseline membrane potential of the bursting neurons. These tonic cells are more properly labeled as bursters that did not have enough $KCa$ current to repolarize them from the bursting plateau. Thus, it is not surprising that these points are located in a region of the conductance map that corresponds more closely to the location of the high burst-rate bursters (Fig. 2D, white points). Fig. 2D shows the best subset of three ionic currents that separates the bursting pattern of activity into different bursting rates. We find that, in this case, the best separation was obtained by a combination of $g_{\max}A$, $g_{\max}Ca$, and $g_{\max}KCa$. Within the bursting region, $g_{\max}KCa$ is extremely important in determining both the rate of bursting and the number of action potentials per burst (Goldman et al., unpublished observations). Thus, we find that a conductance that is relatively unimportant in determining some features of activity can be critically important in determining other features.

## 4. Discussion

We have observed that the large variability in the maximal conductances of measured ionic currents is a natural feature of real cells ([2,4], and see results). Furthermore, we have shown in a conductance-based model that such variability in ionic currents can be consistent with and may indeed enable the production of stable patterns of activity. These results suggest that maintaining activity patterns does not require fine tuning of the properties (i.e. parameters) of each individual ionic current to within narrow limits. Instead, they suggest that activity can be stable over a broad range of parameter values. In the case of our study, this stability can manifest itself in two ways. First, certain individual conductances were found to have relatively little effect on neural firing properties. For example, changes in $g_{\max}KCa$ had very little influence in determining whether a neuron was silent, tonic, or bursting. Such insensitivity to changes in the level of $g_{\mathrm{KCa}}$ was also observed in experimental manipulations of $g_{\mathrm{KCa}}$ in real neurons (Golowasch et al., unpublished observations). Second, certain changes in conductance combinations were found to have little influence due to apparently offsetting effects of the different conductances. Thus, while adding $g_{\max}Ca$ and subtracting $g_{\max}A$ robustly changes the firing state of the model neuron, adding both $g_{\max}Ca$ and $g_{\max}A$ in combination may leave the neuron in the same firing state (Fig. 2A).

We have shown that regulation of activity in a multidimensional conductance-based model occurs at two levels: One in which states of activity, such as silent, tonic firing of action potentials, or bursting, are established in a general manner, and another in which the fine details of a particular state of activity are defined. Certain conductances, such as $g_{\mathrm{Ca}}$ and $g_{\mathrm{A}}$, are important in determining properties on both levels, with an increase of $g_{\max}Ca$ in combination with a decrease in $g_{\max}A$ tending to push cells in a steady progression from silence towards bursting (Fig. 2A),

and from lower voltages (Fig. 2B) or firing rates (Fig. 2C,D) to higher voltages or firing rates, respectively. However, details of bursting are affected by quite different conductances.

Our results have interesting implications for the regulation of activity in biological systems. For instance, while a neuromodulator that evokes a very small ionic current may have a profound effect on the activity pattern generated by a neuron (Golowasch et al., unpublished observations), a different neuromodulator that produces a larger change may have relatively little effect. It has been suggested previously that neural conductance values may lie near such borders to enhance the sensitivity of neurons to neuromodulators that move these conductances across such borders [2]. The broad and relatively well-defined borders that we have found between regions suggests that even neurons with conductances that are widely scattered along such borders can respond in the same, robust manner to the application of a neuromodulator. Thus, variability of conductances can be consistent with both stable firing activity and with stable neuromodulatory action.

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