

1    ***Mechanisms of generation of membrane potential resonance in a***  
2    ***neuron with multiple resonant ionic currents***

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22  
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24    Preferred frequency response; stomatogastric; model neuron, evolutionary algorithm, oscillations

25

## 26 Abstract

27 Neuronal membrane potential resonance (MPR) is associated with subthreshold and network  
28 oscillations. A number of voltage-gated ionic currents can contribute to the generation or amplification  
29 of MPR, but how the interaction of these currents with linear currents contributes to MPR is not well  
30 understood. We explored this in the pacemaker PD neurons of the crab pyloric network. The PD neuron  
31 MPR is sensitive to blockers of H- ( $I_H$ ) and calcium-currents ( $I_{Ca}$ ). We used the impedance profile of the  
32 biological PD neuron, measured in voltage clamp, to constrain parameter values of a conductance-based  
33 model using a genetic algorithm and obtained many optimal parameter combinations. Unlike most cases  
34 of MPR, in these optimal models, the values of resonant- ( $f_{res}$ ) and phasonant- ( $f_{\varphi=0}$ ) frequencies were  
35 almost identical. Taking advantage of this fact, we linked the peak phase of ionic currents to their  
36 amplitude, in order to provide a mechanistic explanation the dependence of MPR on the  $I_{Ca}$  gating  
37 variable time constants. Additionally, we found that distinct pairwise correlations between  $I_{Ca}$   
38 parameters contributed to the maintenance of  $f_{res}$  and resonance power ( $Q_z$ ). Measurements of the PD  
39 neuron MPR at more hyperpolarized voltages resulted in a reduction of  $f_{res}$  but no change in  $Q_z$ .  
40 Constraining the optimal models using these data unmasked a positive correlation between the maximal  
41 conductances of  $I_H$  and  $I_{Ca}$ . Thus, although  $I_H$  is not necessary for MPR in this neuron type, it contributes  
42 indirectly by constraining the parameters of  $I_{Ca}$ .

## 43 Author Summary

44 Many neuron types exhibit membrane potential resonance (MPR) in which the neuron produces the  
45 largest response to oscillatory input at some preferred (resonant) frequency and, in many systems, the  
46 network frequency is correlated with neuronal MPR. MPR is captured by a peak in the impedance vs.  
47 frequency curve (Z-profile), which is shaped by the dynamics of voltage-gated ionic currents. Although  
48 neuron types can express variable levels of ionic currents, they may have a stable resonant frequency.  
49 We used the PD neuron of the crab pyloric network to understand how MPR emerges from the interplay  
50 of the biophysical properties of multiple ionic currents, each capable of generating resonance. We show  
51 the contribution of an inactivating current at the resonant frequency in terms of interacting time  
52 constants. We measured the Z-profile of the PD neuron and explored possible combinations of model  
53 parameters that fit this experimentally measured profile. We found that the Z-profile constrains and  
54 defines correlations among parameters associated with ionic currents. Furthermore, the resonant  
55 frequency and amplitude are sensitive to different parameter sets and can be preserved by co-varying  
56 pairs of parameters along their correlation lines. Furthermore, although a resonant current may be  
57 present in a neuron, it may not directly contribute to MPR, but constrain the properties of other  
58 currents that generate MPR. Finally, constraining model parameters further to those that modify their  
59 MPR properties to changes in voltage range produces maximal conductance correlations.

## 60 Introduction

61 Neuronal network oscillations at characteristic frequency bands emerge from the coordinated activity of  
62 the participating neurons. Membrane potential resonance (MPR) is defined as the ability of neurons to  
63 exhibit a peak in their voltage response to oscillatory current inputs at a preferred or resonant  
64 frequency ( $f_{\text{res}}$ ) [1]. MPR has been observed in many neuron types such as those in the hippocampus [2-  
65 4] and entorhinal cortex [2-6], inferior olive [7, 8], thalamus [1, 9], striatum [10, 11], as well as in  
66 invertebrate oscillatory networks such as the pyloric network of the crustacean stomatogastric ganglion  
67 (STG) [12-14]. Neurons may also exhibit phasonance or a zero-phase response, which describes their  
68 ability to synchronize with oscillatory inputs at a preferred phasonant frequency ( $f_{\phi=0}$ ) [4, 15-18].  
69 Resonance, phasonance and intrinsic oscillations are related, but are different phenomena as one or  
70 more of them may be present in the absence of the others [15, 16, 18].

71 Resonant and phasonant frequencies result from a combination of low- and high-pass filter mechanisms produced  
72 by the interplay of the neuron's passive properties and one or more ionic currents and their interaction with the  
73 oscillatory inputs [1, 15, 18, 19]. The slow resonant currents (or currents having resonant gating variables) oppose  
74 voltage changes and act as high-pass filters. They include the hyperpolarization-activated inward current ( $I_H$ ) and  
75 the slow outward potassium current ( $I_M$ ). On the other hand, the fast amplifying currents (or currents having  
76 amplifying gating variables) favor voltage changes and can make MPR more pronounced. They include the  
77 persistent sodium current ( $I_{NaP}$ ) and the inward rectifying potassium ( $I_{Kir}$ ) current. Most previous systematic  
78 mechanistic studies have primarily examined models with one resonant and one amplifying current, such as  $I_H$  and  
79  $I_{NaP}$ , respectively [15, 18-20]. Currents having both activating and inactivating gating variables (in a multiplicative  
80 way) such as the low-threshold calcium current ( $I_{Ca}$ ) are not included in this classification, but they are able to  
81 produce resonance by mechanisms that are less understood [16, 21].

82 Although a causal relationship between the properties of MPR and network activity has not been established [but  
83 see 22], resonant neurons have been implicated in the generation of network oscillations in a given frequency  
84 band because the resonant and network frequencies often match up or are correlated. One example is in the  
85 hippocampal theta oscillations [23] in which CA1 pyramidal cells exhibit MPR *in vitro* at theta frequencies of 4-10  
86 Hz [2-4, 24] (but see [25]). Interestingly, MPR is not constant across the somatodendritic arbor in these neurons  
87 [26]. Hippocampal interneurons also show MPR *in vitro*, but at gamma frequencies of 30-50 Hz [3, but see 4], and  
88 gamma oscillations have been found to be particularly robust in network models containing resonant interneurons  
89 [27, 28].

90 The crab pyloric network produces stable oscillations at a frequency of ~1 Hz, driven by a pacemaker  
91 group composed of two neuron types, the anterior burster (AB) and the pyloric dilator (PD), that  
92 produce synchronized bursting oscillations through strong electrical-coupling [29]. The PD neuron shows  
93 MPR, with  $f_{\text{res}} \sim 1$  Hz that is positively correlated with the pyloric network frequency [12]. Previous work  
94 has demonstrated that MPR in this neuron depends on two voltage-gated currents:  $I_{\text{Ca}}$  and  $I_{\text{H}}$  [12]. Ionic  
95 current levels in pyloric neurons are highly variable across animals, even in the same cell type [30]. It is  
96 therefore unclear how these currents may interact to produce a stable MPR in the PD neuron and  
97 whether this variability persists or is increased or decreased in the presence of oscillatory inputs.

98 Traditionally, MPR is measured by applying ZAP current injection and recording the amplitude of the voltage  
99 response [1, 31]. In some systems, depolarization can increase [32] or decrease [33], 1996 the preferred  
100 frequency. Alternatively, resonance is measured by applying ZAP voltage inputs in voltage clamp and recording the  
101 amplitude of the total current. Both approaches yield identical results for linear systems, but not necessarily for  
102 nonlinear systems. A previous study from our lab using the voltage clamp technique showed that in the PD neuron  
103 hyperpolarization decreases both  $f_{\text{res}}$  and network frequencies [14]. Since MPR results from the outcome of the  
104 dynamics of voltage-gated ionic currents activated in different voltage ranges, changing the input voltage  
105 amplitude is expected to change  $f_{\text{res}}$  in an input amplitude-dependent manner. This cannot be captured by linear  
106 models in which impedance is independent of the input amplitude. To our knowledge, no study has attempted to  
107 understand the ionic mechanisms that produce shifts in  $f_{\text{res}}$  in response to changes in the voltage range.

108 Previous studies have explored the generation of MPR by  $I_{\text{Ca}}$  and through the interaction between  $I_{\text{Ca}}$   
109 and  $I_{\text{H}}$  in hippocampal CA1 pyramidal neurons [16, 17] and thalamic neurons [21], where the resonant  
110 and network frequencies are significantly higher than in the crab pyloric network and the  $I_{\text{Ca}}$  time  
111 constants are smaller. Based on numerical simulations, these investigations have produced important  
112 results about the role of the activating and inactivating gating variables and their respective time  
113 constants play in the generation of MPR and the determination of  $f_{\text{res}}$ . However, a mechanistic  
114 understanding of the effects of the interacting time constants and voltage-dependent inactivation that  
115 goes beyond simulations is lacking. An important finding for the CA1 pyramidal neurons is that, for  
116 physiological time constants, they exhibit resonance, but no phasonance [16]. However, for larger time  
117 constants, outside the physiological range for these neurons, they are able to exhibit phasonance. This  
118 suggests that PD neurons, which have slower time scale currents, may exhibit resonance and  
119 phasonance at comparable frequencies. If so, such a correlation between resonance and phasonance  
120 can be used to explain the influence of ionic current parameters.

121 Our study has two interconnected goals: (i) to understand how the interplay of multiple resonant gating  
122 variables shapes the Z- and  $\phi$ -profiles (impedance amplitude and phase-shift as a function of input  
123 frequency) of a biological PD neuron, and (ii) to understand the many ways in which these interactions  
124 can occur to produce the same Z-profile in these neurons. For a neuron behaving linearly, e.g., with  
125 small subthreshold inputs, this task is somewhat simplified by the fact that linear components are  
126 additive. However, neurons are nonlinear and the nonlinear interaction between ionic currents has been  
127 shown to produce unexpected results [16, 18, 19].

128 To achieve these goals we measured and quantified the Z- and  $\phi$ -profiles of the PD neuron. We then  
129 used a single-compartment conductance-based model of Hodgkin-Huxley type [34] that included a  
130 passive leak and the two voltage-gated currents  $I_H$  and  $I_{Ca}$  to explore what combinations of model  
131 parameters can produce the experimentally observed PD neuron Z- and  $\phi$ -profiles. The maximal  
132 conductances of ionic currents of neurons in the stomatogastric nervous system vary widely [35-37]. We  
133 therefore assume that the parameters that determine the Z-profile in the PD neuron vary across  
134 animals. Thus, instead of searching for a single model that fit the PD neuron Z-profile, we used a genetic  
135 algorithm to capture a collection of parameter sets that fit this Z-profile. To achieve such a fit, we  
136 defined a set of ten attributes that characterize the PD neuron Z-profile (e.g., resonant frequency and  
137 amplitude) and used a multi-objective evolutionary algorithm [MOEA, 38] to obtain a family of models  
138 that fit these attributes. We then used this family of optimal models to identify the important  
139 biophysical parameters and relationships among these parameters to explain how the PD neuron Z-  
140 profile is shaped. We show how the fact that the inactivating calcium current peaks at the same phase  
141 as the passive properties, in response to sinusoidal inputs, can explain why resonant and phasonant  
142 frequencies are equal. We identify significant pairwise parameter-correlations, which selectively set  
143 certain attributes of MPR. We show that, in this neuron,  $I_H$  does not produce MPR but can extend the  
144 dynamic range of  $I_{Ca}$  parameters mediating MPR. Furthermore, we identify a subset of models that  
145 capture the experimental shift in the resonant frequency with changes in lower bound of voltage  
146 oscillation. Finally, we exploit the fact that the resonant and phasonant frequencies are equal for the PD  
147 neuron to provide a mechanistic understanding of the effects of the  $I_{Ca}$  time constants on the resonant  
148 frequency by using phase information. Our results provide a mechanistic understanding for a generic  
149 class of neurons that exhibit both resonance and phasonance as the result of the interaction between  
150 multiplicative gating variables and complement the studies in [16].

151 **Results**

152 The PD neuron produces 1 Hz bursting oscillations with a slow-wave approximately -60mV to -30mV (fig  
153 3a). Driving the neuron through this voltage range with a ZAP function in voltage clamp (fig 3b top  
154 panel) produces a minimum (arrow in fig 3b bottom panel) in the amplitude of the current response  
155 (fig 3b). The input frequency at which this minimum occurs corresponds to a peak in the Z-profile ( $f_{res}$ ,  
156  $Z_{max}$ ; fig 3c1). The value of  $f_{res}$  was  $0.86 \pm 0.05$ Hz producing  $Z_{max}$  values of  $10.23 \pm 0.51$  MΩ (N = 18; fig  
157 3d). The  $\phi$ -profile shows a phasor frequency  $f_{\phi=0} = 0.81 \pm 0.05$ Hz, which in most cases matched  $f_{res}$   
158 (fig 3c2). The PD neuron had a  $Q_Z$  of  $2.77 \pm 0.71$  MΩ and  $\Lambda_{\%}$  of  $0.53 \pm 0.04$  Hz. Across preparations,  $Q_Z$   
159 showed considerable variability, whereas  $f_{res}$ ,  $\Lambda_{\%}$ , and  $f_{\phi=0}$  were relatively consistent (fig 3d). The  
160 corresponding median values for  $f_{res}$ ,  $Q_Z$ ,  $\Lambda_{\%}$ , and  $f_{\phi=0}$  were 0.83 Hz, 2.77 MΩ, 0.5 Hz, 0.79 Hz,  
161 respectively.

162 To obtain model parameter combinations constrained by the PD neuron Z- and  $\phi$  - profiles, we  
163 generated a population of models using an NSGA-II algorithm (see Methods). The attributes of a single  
164 PD neuron Z- and  $\phi$  -profiles (fig 4, filled red circles) constrained the optimization of the parameter  
165 values. This resulted in a population of ~9000 sets of parameters (“optimal” dataset). All models in the  
166 optimal dataset captured the attributes of Z and  $\phi$  to within 5% of the target (light blue lines in fig 4),  
167 with the exception of  $\phi_{max}$ , which may be due to the anatomical structure of the PD neuron, a property  
168 that is omitted in our single-compartment model, or due to additional ionic currents, such as the  
169 potassium A current, which are not included in our model [16, 39].

170 **The generation of MPR by the interaction of two resonant voltage-gated currents**

171 To understand how Z is generated by the dynamics of individual ionic currents at different voltages and  
172 frequencies, we examined the amplitude and kinetics of ionic currents. In voltage clamp, Z is shaped by  
173 active voltage-gated currents, interacting with the passive leak and capacitive currents, in response to  
174 the voltage inputs. To understand the contribution of different ionic currents, we measured these  
175 currents in response to a constant frequency sine wave voltage inputs (fig 5a inset) at three frequencies:  
176 0.1Hz, 1Hz ( $f_{res}$ ) and 4Hz (fig 5). For these frequencies, we plotted the steady-state current as a function  
177 of voltage (fig 5b-d left) and normalized time (or cycle phase = time x frequency; fig 5b-d right). At 0.1  
178 Hz, the amplitudes of  $I_H$  and  $I_L + I_{Cm}$  sets  $I_{total}$  at low (~ -60 mV) and high (~ -30 mV) voltages, respectively  
179 (fig 5b left). Since  $I_H$  deactivation is slow, it also contributes to  $I_{total}$  at high voltages (fig 5b right). At 1 Hz

180 ( $=f_{\text{res}}$ ),  $I_H$  still sets the minimum of the total current, but, because of its slow kinetics, its steady-state  
181 dynamics are mostly linear (fig 5c left). However, now  $I_{\text{Ca}}$  peaks in phase (fig 5c right) with the passive  $I_L +$   
182  $I_{\text{Cm}}$  at high voltages, thus producing a smaller  $I_{\text{total}}$  (magenta bar in fig 5c). The values of  $I_H$  at 4 Hz are not  
183 much different from 1 Hz (fig 5d). However,  $I_{\text{Ca}}$  peaks at a much later phase (fig 5d right), which does not  
184 allow it to compensate for  $I_L + I_{\text{Cm}}$  at high voltages, thus resulting in a larger  $I_{\text{total}}$  (magenta bar in fig 5d).  
185 Note that at 1 Hz, the total current peaks at a cycle phase close to 0.5, thus implying that that the  $f_{\text{res}}$   
186 and  $f_{\phi=0}$  are very close or equal (fig 5c right). Although figure 5 shows the results for only one model in  
187 the optimal dataset, these results remain nearly identical for all models in the optimal dataset. The  
188 standard deviation of the currents measured, including the total current was never above 0.15 nA over  
189 all models. The inset in fig. 5c shows one standard deviation around the mean for the data shown in the  
190 right panel, calculated for 200 randomly selected models.

191 An important collective property of the models we found is that the two frequencies,  $f_{\text{res}}$  and  $f_{\phi=0}$   
192 coincide (fig. 6a-b). We analyzed the experimental data, and confirmed that the coincidence of MPR and  
193 phasonance frequencies also occurs in the biological system (fig. 6b inset). This is typically not the case  
194 for neuronal models (and for dynamical systems in general), not even for linear systems [18-20], with  
195 the exception of the harmonic oscillator. However, the fact that it occurs in this system, allows us to use  
196 the current vs. cycle phase (current-phase) diagrams to understand the dependence of  $f_{\text{res}}$  and  $f_{\phi=0}$  on  
197 the model parameters (fig. 6c).

198 The current-phase diagrams are depicted as in fig 5b-d, as graphs of  $I_{\text{total}}$ ,  $I_L$  and  $I_{\text{Ca}}$  as a function of the  
199 cycle phase for each given specific input frequency (fig. 6c). We do not show  $I_H$  and  $I_{\text{Cm}}$  in this plot,  
200 because at frequencies near  $f_{\text{res}}$  they do not change much with input frequency. Note that  $I_L$  is  
201 independent of the input frequency (five panels in fig. 6c) because it precisely tracks the input voltage.

202 In voltage clamp,  $f_{\phi=0} = 1\text{Hz}$  is where  $I_{\text{total}}$  is at its minimum amplitude exactly at cycle phase 0.5,  
203 coinciding with the peak of the input voltage (fig. 6c, middle). The fact that  $I_L$  precisely tracks the input  
204 voltage imposes a constraint on the shapes of  $I_{\text{Ca}}$  and  $I_{\text{total}}$ . Therefore, by necessity, if the  $I_{\text{Ca}}$  trough  
205 occurs for a cycle phase below 0.5, the  $I_{\text{total}}$  peak must occur for a cycle phase above 0.5 (fig. 6c, top two  
206 panels) and vice versa (fig. 6c, bottom two panels). This is shown by the slope of the line joining the  
207 peaks of  $I_{\text{total}}$  and  $I_{\text{Ca}}$  and, at  $f_{\text{res}}$  this line is approximately vertical (fig. 5c middle panel).

208 We use this tool to explain the dependence of the Z-profile on the time constants  $\tau_m^{\text{Ca}}$  (fig. 7a) and  $\tau_h^{\text{Ca}}$   
209 (fig. 7b). The corresponding current-phase diagrams are presented in figs. 7c and 7d, respectively. In

210 each panel we present the current-phase diagrams for  $f$  at 1 Hz ( $=f_{\text{res}}$  when the parameter is at 100%;  
211 middle) and  $f=f_{\text{res}}$  (sides) when  $f_{\text{res}}$  is different from 1Hz.

212 To understand the dependence of  $Z$  on changes in  $\tau_m^{\text{Ca}}$  and  $\tau_h^{\text{Ca}}$  we have to primarily explain the  
213 dependence of the two attributes  $Z_{\text{max}}$  and  $f_{\text{res}}$  on these parameters. While  $f_{\text{res}}$  has a similar monotonic  
214 dependence on  $\tau_m^{\text{Ca}}$  and  $\tau_h^{\text{Ca}}$  (as these parameters increase,  $f_{\text{res}}$  decreases),  $Z_{\text{max}}$  has the opposite  
215 dependence on  $\tau_m^{\text{Ca}}$  and  $\tau_h^{\text{Ca}}$ . The opposite dependence of  $Z_{\text{max}}$  on  $\tau_m^{\text{Ca}}$  and  $\tau_h^{\text{Ca}}$  is a straightforward  
216 consequence of the opposite feedback effects (positive for  $\tau_m^{\text{Ca}}$  and negative for  $\tau_h^{\text{Ca}}$ ) that these  
217 parameters exert on  $I_{\text{Ca}}$ . An increase in  $\tau_m^{\text{Ca}}$  (for fixed values of  $\tau_h^{\text{Ca}}$ ) results in a smaller  $I_{\text{Ca}}$  in response to  
218 a given voltage clamp input. Because  $I_{\text{Ca}}$  is smaller and negative, this leads to an increase in  $I_{\text{total}}$  and a  
219 decrease in  $Z$  at all frequencies. Similarly, an increase in  $\tau_h^{\text{Ca}}$  (for fixed values of  $\tau_m^{\text{Ca}}$ ) results in a larger  $I_{\text{Ca}}$ ,  
220 leading to a decrease in  $I_{\text{total}}$  and an increase in  $Z$ .

221 For a fixed value of the input frequency  $f$  (e.g.  $f=1$  Hz as in fig. 7), for  $Z_{\text{max}}$  to decrease as  $\tau_m^{\text{Ca}}$  increases  
222 (fig. 7-a), the cycle phase of peak  $I_{\text{Ca}}$  is delayed thereby subtracting less from  $I_L$  on the depolarizing  
223 phase. This leads to  $I_{\text{total}}$  to phase advance relative to  $I_L$  (fig. 7-c) and causes  $f_{\text{res}}$  to decrease. Similarly, for  
224  $Z_{\text{max}}$  to increase as  $\tau_h^{\text{Ca}}$  increases (fig. 7-b),  $I_{\text{Ca}}$  has to peak later in the cycle thereby subtracting less from  
225  $I_L$  on the depolarizing phase, which causes  $I_{\text{total}}$  to peak earlier in the cycle, which in turn causes the bar  
226 also to swing from the left to the right (fig. 7-d). Therefore,  $f_{\text{res}}$  decreases.

227

## 228 Parameter constraints and pairwise correlations

229 Previous studies have shown that stable network output can be produced by widely variable ion channel  
230 and synaptic parameters [37, 40]. Our biological data, similarly, showed that many of the  $Z$ - and  $\phi$ -  
231 profile attributes, such as  $f_{\text{res}}$ ,  $\Lambda_{1/2}$  and  $f_{\phi=0}$  are relatively stable across different PD neurons whereas  $Q_Z$   
232 shows the most variability (fig 3d). To determine whether the  $Z$ - and  $\phi$ -profile attributes constrain ionic  
233 current parameters, we examined the variability of the model parameters in the optimal dataset. We  
234 found that some parameters were more constrained while others were widely variable, as measured by  
235 the coefficient of variation (CoV; fig 8a). Parameters showing large CoVs were  $\bar{g}_{\text{Ca}}$ ,  $\tau_m^h$ ,  $\bar{g}_h$ ,  $\tau_h^{\text{Ca}}$ , and  
236  $V_{1/2}^{\text{Ca},h}$ ; those showing small CoVs were  $\bar{g}_L$  and the time constant of activation of  $I_H$  and  $I_{\text{Ca}}$  and half-

237 activation voltage of  $I_{Ca}$ :  $\tau_m^{Ca}$ ,  $V_{1/2}^{Ca_m}$ ,  $\bar{g}_L$  (in increasing order of CoV value). A small CoV value implies that  
238 the parameter is tightly constrained in order to produce the proper Z- and  $\varphi$ -profiles.

239 A number of studies have indicated that the large variability in ion channel parameters is counter-  
240 balanced by paired linear covariation of these parameters [36, 37, 41-43]. Considering the large  
241 variability, we identified parameter pairs that co-varied (fig 8b). For this, we carried out a permutation  
242 test for the Pearson's correlation coefficients, followed by a Student's t-test on the regression slopes, to  
243 identify significant correlations between pairs of parameters (see Methods). The strongest correlations  
244 were between the following parameters:  $\bar{g}_L - \bar{g}_H$  ( $r=-0.93$ ),  $\bar{g}_L - \tau_m^{Ca}$  ( $R = 0.73$ ),  $\bar{g}_L - \tau_h^{Ca}$  ( $R = 0.88$ ),  
245  $\bar{g}_H - \tau_m^H$  ( $R = 0.68$ ),  $\bar{g}_H - \tau_h^{Ca}$  ( $R = -0.82$ ),  $\bar{g}_H - V_{1/2}^{Ca_h}$  ( $R = 0.76$ ),  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  ( $R = -0.94$ ), and  $\tau_m^{Ca} - \tau_h^{Ca}$  ( $R = -0.80$ )  
246 (correlations selected with  $p < 0.01$ ; fig 8b).

247 In our experiments,  $V_{1/2}^{H_m}$  was fixed at -70 mV, using data from experimental measurements in crab [44]  
248 (see Methods). However, we also repeated the MOEA with  $V_{1/2}^{H_m}$  set to -96 mV, as reported in lobster  
249 experiments [45], and found that all correlations observed with the former value of  $V_{1/2}^{H_m}$  remain intact,  
250 but simply with a much larger maximal conductance of  $I_H$  (fig. S1). In other words, shifting  $V_{1/2}^{H_m}$  to the left  
251 simply results in larger  $\bar{g}_H$  in the optimal models without qualitatively changing the other findings.

252 In particular, we found that the  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  correlation appeared nonlinear, but there were strong and  
253 distinct linear correlations in the two regions  $\bar{g}_{Ca} > 0.05 \mu\text{S}$  (low  $\bar{g}_{Ca}$ ) and  $\bar{g}_{Ca} < 0.05 \mu\text{S}$  (high  $\bar{g}_{Ca}$ ; fig  
254 8c). To ensure that our partitioning of the population into different levels of  $\bar{g}_{Ca}$  was valid, we ran the  
255 MOEA two additional times, each time using only the mean values of  $\bar{g}_L$ ,  $\tau_m^H$ ,  $V_{1/2}^{Ca_m}$ , and  $\tau_m^{Ca}$  for either  
256 the low or the high  $\bar{g}_{Ca}$  values. These optimal models consistently separated into two non-overlapping  
257 model parameters, consistent with the low and high  $\bar{g}_{Ca}$  models in fig 8c.

258 We examined if the low and high  $\bar{g}_{Ca}$  models separated or showed distinct correlations in the remaining  
259 parameters. The two groups produced non-overlapping subsets of model parameters in the  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$   
260 graph. We calculated the Pearson's correlation coefficient for each pair of parameters in the low and  
261 high  $\bar{g}_{Ca}$  groups and tested for significance as before (see Table 2). We found that only the high  $\bar{g}_{Ca}$   
262 group showed a significant  $\tau_m^{Ca} - \tau_h^{Ca}$  and  $\bar{g}_H - \tau_h^{Ca}$  correlations (Table 2). Additionally, both low and high

263  $\bar{g}_{Ca}$  groups showed the following correlations:  $V_{1/2}^{Ca^h} - \tau_h^{Ca}$ ,  $\bar{g}_L - \bar{g}_H$ ,  $\bar{g}_{Ca} - V_{1/2}^{Ca^h}$ , and  $\bar{g}_H - \tau_m^H$ ,  $\bar{g}_{Ca} - \tau_h^{Ca}$ .

264 Furthermore, when we ran the MOEA on models where  $\bar{g}_H$  was set to 0, the only optimal models

265 obtained fell within a narrow range of the high  $\bar{g}_{Ca}$  group (fig S2), which is consistent with the

266 distribution of high  $\bar{g}_{Ca}$  models in the  $\bar{g}_H - \bar{g}_{Ca}$  panel of figure 8d.

267

268 Decreasing the lower bound of voltage oscillations influences the measured  $f_{res}$   
269 and  $Z_{max}$

270 The lower voltage range of the PD bursting oscillation is strongly influenced by the inhibitory synaptic input from  
271 the lateral pyloric neuron (LP), and previous work has shown that  $f_{res}$  in the PD neuron is influenced by the  
272 minimum of the voltage oscillation ( $V_{low}$ ) [14]. In order to explore which subset of our optimal models faithfully  
273 reproduce the influence of the minimum voltage range, we measured the Z-profile when  $V_{low}$  was changed from -  
274 60 to -70 mV (fig 9a). Decreasing  $V_{low}$  significantly decreased  $f_{res}$  (by  $0.24 \pm 0.8$  Hz), while there was no significant  
275 difference in the mean  $Z_{max}$  ( $-0.15 \pm 0.81$  MΩ) (two-way RM-ANOVA;  $N = 8$ ,  $p < 0.001$ ; fig 9b, left panel).

276 To explore whether the shift in  $f_{res}$  as a function of  $V_{low}$  could be captured by either low or high  $\bar{g}_{Ca}$  models, we  
277 measured the shift in  $f_{res}$  and  $Z_{max}$ , when  $V_{low}$  was changed from -60mV to -70mV. We found that  $f_{res}$  decreased by  
278  $0.24 \pm 0.03$  Hz and  $Z_{max}$  increased by  $5.2 \pm 0.6$  MΩ for high  $\bar{g}_{Ca}$  models, whereas  $f_{res}$  decreased by  $0.07 \pm 0.02$  Hz and  
279  $Z_{max}$  decreased by  $2.6 \pm 0.2$  MΩ for low  $\bar{g}_{Ca}$  models (fig 9b, right panel). Therefore, neither model group reproduced  
280 the experimental changes in the Z-profile, specifically, a decrease in  $f_{res}$  and no change in  $Z_{max}$ .

281 We consequently filtered the full optimal dataset (black dots fig 9c) to find a subset of models that reproduced the  
282 change in  $f_{res}$  and  $Z_{max}$  (to within 5% of the representative experimental Z(f) shown in fig 9a) when  $V_{low}$  was  
283 decreased to -70mV. Of the ~9000 models in the population, we found ~1000 models that produced the desired  
284 change. Interestingly, the resulting models showed a trade-off in values for  $\bar{g}_{Ca}$  and  $V_{1/2}^{Ca^h}$  parameters that showed  
285 little overlap with the low and high  $\bar{g}_{Ca}$  model groups (fig 9c).

286 To understand why this particular group (which we will term intermediate  $\bar{g}_{Ca}$ ) produced small changes in  $Z_{max}$   
287 when  $V_{low}$  was decreased, we plotted the current-voltage relationships for  $I_{Ca}$ ,  $I_H$ ,  $I_{Ca}+I_H$  and  $I_{total}$  for  $V_{low} = -60$  and -  
288 70 mV, measured at  $f=1$ Hz ( $f_{res}$  at  $V_{low} = -60$ mV) and compared these models with the low and high  $\bar{g}_{Ca}$  models. For  
289  $V_{low} = -60$ mV, the ionic currents behaved similarly for all model groups and  $I_{total}$  was maximal at -30mV (magenta  
290 curve in fig 9d1-3), indicating the similarity of all models in the optimal dataset. However, when  $V_{low}$  was at -70mV

291 revealed differences in peak  $I_{Ca}$ , without affecting the peak amplitude of  $I_H$  across the different  $\bar{g}_{Ca}$  groups (fig  
292 9e1-3). The differences in peak  $I_{Ca}$  accounted for most of the changes in  $I_{total}$  across the different  $\bar{g}_{Ca}$  groups. The  
293  $Z_{max}$  values for intermediate  $\bar{g}_{Ca}$  models reproduced the small shift seen in experiments because  $I_{Ca}$  were at the  
294 correct level at high voltages (-30 mV) when  $V_{low}$  was at -70mV (fig 9e3). The other two groups did not produce  
295 appropriate  $Z_{max}$  for  $V_{low} = -70$ mV because either  $I_{Ca}$  was too small (and hence  $I_{total}$  too large), resulting in a smaller  
296  $Z_{max}$  (fig 9e1) or vice versa (fig 9e2). It was also clear that the more negative voltages allowed for an increase in  $I_H$   
297 levels and therefore larger contribution to the total current. With  $V_{low}$  at -70mV, not only was there a larger peak  
298 amplitude of  $I_H$  at the lower voltages, but the current at positive voltages also increased because of the very slow  
299 deactivation rate. Consequently,  $I_H$  did not fully turn off when  $I_{Ca}$  peaked, so that it also contributes to shaping the  
300 upper envelope of the total current.  $I_H$  kinetics were different across the groups (fig 9e1-e3). Taken together with  
301 the fact that when  $I_H$  was removed produced only parameter values with very high  $\bar{g}_{Ca}$  and very low  $V_{1/2}^{Ca^h}$  (fig S1),  
302 these data suggest that  $I_H$  could extend the range of  $I_{Ca}$  parameters over which MPR through compensation for  
303 variable levels of  $I_H$ .

304 The  $I_{Ca}$  in low  $\bar{g}_{Ca}$  models was too small when  $V_{low}$  was -70 mV, because the low conductance did not allow for a  
305 significant contribution from the additional de-inactivation (considering the higher  $V_{1/2}^{Ca^h}$  in this group) and  
306 therefore the peak current did not increase enough. Consequently, the contribution of  $I_H$  at low voltages was  
307 greater than that of  $I_{Ca}$  at higher voltages (fig 9e2). Conversely, in the high  $\bar{g}_{Ca}$  group,  $V_{1/2}^{Ca^h}$  was more negative and  
308 so many more channels were available for de-inactivation and the contribution of  $I_{Ca}$  at higher voltages was much  
309 larger than that of  $I_H$  at low voltages (fig 9e3). These findings suggest that the balance between these two currents,  
310 that shape the lower and upper envelope of the total current response to voltage inputs, is necessary to produce  
311 the appropriate shift in  $f_{res}$  without influencing  $Z_{max}$  significantly.

312 The intermediate  $\bar{g}_{Ca}$  models were strongly correlated in  $\bar{g}_{Ca} - V_{1/2}^{Ca^h}$  ( $R^2 = 0.89$ ;  $p < 0.001$  fig 9f1, and had a  
313 stronger correlation in the  $\tau_m^{Ca} - \tau_h^{Ca}$  parameters compared to all models ( $R^2 = 0.65$ ;  $p < 0.001$ ; fig 9g). Limiting the  
314 optimal models to the intermediate  $\bar{g}_{Ca}$  group also revealed a correlation in the  $\bar{g}_{Ca} - \bar{g}_H$  parameters ( $R^2 = 0.79$ ;  $p <$   
315  $0.001$ ; fig 9h). This new correlation may be produced by the balance of the amplitudes of  $I_H$  and  $I_{Ca}$  at the lower and  
316 higher voltages, respectively.

317

318  $f_{res}$  and  $Q_z$  are maintained by distinct pairwise correlations

319 To determine if any of the MPR attributes were sensitive to the correlations, we ran a 2D sensitivity  
320 analysis on a random subset of 50 models. We tested for significant difference in sensitivity across low,  
321 intermediate and high levels of  $\bar{g}_{Ca}$ . In particular, we tested for significant sensitivity of  $f_{res}$  and  $Q_z$  when  
322 parameters were co-varied in directions parallel ( $L$ ) or perpendicular ( $L^\perp$ ) to their respective population  
323 correlation lines.

324 We first examined whether  $f_{res}$  and  $Q_z$  were sensitive to  $\tau_m^{Ca} - \tau_h^{Ca}$  for both high (fig 10a1), low (fig 10a2),  
325 and intermediate  $\bar{g}_{Ca}$  (fig 10a3) when parameters were moved along  $L$  and  $L^\perp$  (blue and green line; fig  
326 10a1-a3). For high and intermediate  $\bar{g}_{Ca}$  models,  $f_{res}$  sensitivities in the  $L$  group were negative and not  
327 significantly different (3-way RM ANOVA; N=50, p > 0.05), but both groups were significantly different  
328 from the low  $\bar{g}_{Ca}$  group (3-way RM ANOVA; N=50, p < 0.001), which had a positive sensitivity (fig 10b).  
329 This result indicates that the correlation did a better job at maintaining the value of  $f_{res}$  when the value  
330 of  $\bar{g}_{Ca}$  is intermediate or high. For all  $\bar{g}_{Ca}$  groups, we found that there was a significant interaction  
331 between the Z attribute and direction (2-way RM ANOVA; F(1, 49) = 853.52, p < 0.001). When carrying  
332 out a pairwise comparison for each direction within an attribute, we found a significant difference in  
333 sensitivity between  $L$  and  $L^\perp$  for  $f_{res}$  ( $t(93.57)=28.251$ , p<0.001). Similarly, for all  $\bar{g}_{Ca}$  groups, significant  
334 difference in sensitivity between  $L$  and  $L^\perp$  for  $Q_z$  ( $t(93.57)=-8.294$ , p<0.001). Because the difference  
335 between  $L$  and  $L^\perp$  for  $Q_z$  was negative, these results suggest that the  $\tau_m^{Ca} - \tau_h^{Ca}$  correlation determines  $f_{res}$   
336 and not  $Q_z$  (fig 10b).

337 We next examined whether  $f_{res}$  and  $Q_z$  were sensitive to the  $\bar{g}_{Ca} - V_{1/2}^{Ca^h}$  correlation for the three model  
338 groups (fig 11a1-3). For all  $\bar{g}_{Ca}$  groups, we found that there was a significant interaction between the Z  
339 attribute and direction (2-way RM ANOVA; F(1, 49) = 1262.73.2, p < 0.001). When carrying out a  
340 pairwise comparison for each direction within an attribute, we found a significant difference in  
341 sensitivity between  $L$  and  $L^\perp$  for  $f_{res}$  ( $t(95.18)=10.10$ , p<0.001). Similarly, for all  $\bar{g}_{Ca}$  groups, we found a  
342 significant difference in sensitivity between  $L$  and  $L^\perp$  for  $Q_z$  ( $t(95.18)=-35.62$ , p<0.001). Therefore, these  
343 results suggest that the  $\bar{g}_{Ca} - V_{1/2}^{Ca^h}$  correlation determines  $Q_z$  and not  $f_{res}$  (fig 11b).

344 Finally, we tested the sensitivity of  $f_{res}$  and  $Q_z$  to the  $\bar{g}_{Ca} - \bar{g}_H$  correlation in the intermediate  $\bar{g}_{Ca}$  group  
345 (fig 12a). We found that there was a significant interaction between the Z attribute and direction (2-way  
346 RM ANOVA; F(1, 11.12) = 2236.2, p < 0.001). When carrying out pairwise comparisons between

347 directions for each attribute, we found there was a significant difference in  $f_{res}$  sensitivity between L  
348 and  $L^\perp$  ( $t(93.93) = 2.65, p = 0.0095$ ; fig 12). Although the sensitivity of  $Q_z$  was not 0 for L, the difference  
349 in sensitivity values between L and  $L^\perp$  was also significantly different ( $t(93.93) = 62.157, p < 0.0001$ ; fig  
350 12b). These results suggest that, when  $V_{low}$  is at -70 mV, for this subset of models to shift  $f_{res}$  with only  
351 small shifts in  $Z_{max}$ ,  $\bar{g}_H$  and  $\bar{g}_{Ca}$  values must be balanced. It may be possible that the  $Q_z$  sensitivity is not  
352 closer to zero along L because  $V_{1/2}^{Ca^h}$ , which is also negatively correlated with  $\bar{g}_{Ca}$ , should decrease too to  
353 compensate for changes in  $Q_z$ .

354

## 355 Discussion

356 Many neuron types exhibit membrane potential resonance (MPR) in response to oscillatory inputs.  
357 Several studies have shown that the resonant frequency of individual neurons is correlated with the  
358 frequency of the network in which they are embedded [2, 6, 12, 14, 22, 46]. Moreover, networks of  
359 resonant neurons have been proposed to generate more robust network oscillations than neurons with  
360 low-pass filter properties [27, 28]. In several cases, the underlying nonlinearities and time scales that  
361 shape the Z-profile also shape specific properties of the spiking activity patterns, thus leading to a link  
362 between the subthreshold and suprathreshold voltage responses [25, 47].

363 Previous work in the crustacean stomatogastric pyloric network has shown that the resonance  
364 frequency of the pyloric pacemaker PD neurons is correlated with the pyloric network frequency and is  
365 sensitive to blockers of both  $I_H$  and  $I_{Ca}$  [12-14]. However, it was not clear how these voltage-gated ionic  
366 currents and the passive properties could interact to generate MPR in the PD neurons. Previous  
367 modeling work showed that these currents participate in the generation of resonance in CA1 pyramidal  
368 neurons [16, 17]. However, due to the differences in  $I_{Ca}$  time constants, the interaction between its  
369 activating and inactivating gating variables did not produce phasorance in CA1 pyramidal neurons, while  
370 it does in PD neurons. On a more general level, it is not well understood how the nonlinear properties of  
371 ionic currents affect their interplay. Previous studies have shown such interactions may lead to  
372 unexpected results, which are not captured by the corresponding linearizations [16-19]. This complexity  
373 is expected to increase when two currents with resonant components are involved [16, 48]. We  
374 therefore set out to investigate the biophysical mechanism underlying such interactions by using a  
375 combined experimental and computational approach and the biological PD neuron as a case study. The  
376 two PD neurons are electrically coupled to the pacemaker anterior burster neuron in the pyloric  
377 network and their MPR directly influences the network frequency through this electrical coupling [22].  
378 Consequently, our findings have a direct bearing on how the pyloric network frequency is controlled.

379 Many studies of biophysical models have explored the parameter space using a brute-force technique,  
380 by sampling the parameters on a grid [40, 49]. Although this technique provides a rather exhaustive  
381 sampling of the parameter space, using a fine grid on a large number of free parameters could lead to  
382 combinatorial explosion and result in a prohibitive number of simulations. On the other hand, a sparse  
383 sampling may miss “good” solutions. A multi-objective evolutionary algorithm (MOEA) can generate  
384 multiple trade-off solutions in a single run and can handle large parameter spaces very well. In contrast

385 to a brute-force approach, the MOEA can potentially cover a much larger range with possibly hundreds  
386 of values [38]. One disadvantage of the MOEA is that, as the number of objectives increases, the search  
387 may miss a large portion of the parameter space. This occurs because randomly generated members  
388 often tend to be just as good as others, which means that the MOEA would run out of room to introduce  
389 new solutions in a given generation. To try to overcome this problem, we carefully chose the parameters  
390 of the MOEA such as population size, mutation and crossover distribution indices (100, 20 and 20,  
391 respectively) and ensured that the sampled population covered the parameter space evenly.  
392 Additionally, we ran the MOEA multiple times, each time collecting all the good parameter sets until one  
393 has exhausted all regions of the parameter space where good models exist.

394 In previous work, we and other authors have examined how the additive interaction of ionic currents  
395 with resonant and amplifying gating variables shape the Z and  $\phi$  profiles at both the linear and nonlinear  
396 levels of description [6, 15, 18, 20, 32, 33, 50]. However, the role of inactivating currents in the  
397 generation of MPR is not so clear. Authors have established that  $I_{Ca}$  can generate MPR in the absence of  
398 additional ionic currents [21], that the activation variable diminishes the propensity for MPR and the  
399 interaction with  $I_H$  enhances the dynamic range of parameters producing  $I_{Ca}$ -mediated resonance [16].  
400 Even so, to date, only a descriptive explanation of how the ionic current parameters affect certain  
401 attributes of MPR has been provided, but no study has provided a mechanistic understanding in terms  
402 of the parameters of  $I_{Ca}$  that go beyond numerical simulations.

403 Similar to [16], the model we used in this paper involves the interaction between resonant and  
404 amplifying components. Specifically, this model includes a calcium current with both activation  
405 (amplifying) and inactivation (resonant) gating variables, and an H-current with a single activation  
406 (resonant) gate. Since  $I_H$  and  $I_{Ca}$  shape the lower and upper envelopes of the voltage response to current  
407 inputs, respectively [12], given the appropriate voltage-dependence and kinetics of the currents both  
408 could play equal roles at different voltage ranges. In fact, either  $I_{Ca}$  inactivation or  $I_H$  is capable of  
409 producing MPR [2, 21]. In CA1 pyramidal neurons, the differences in Z profiles are due to the passive  
410 properties and the kinetics of  $I_H$  [4]. It is possible that the kinetic parameters of  $I_H$  and  $I_{Ca}$  are tuned so  
411 that they contribute nearly equally to shaping the envelopes of the voltage-clamp current.

412 By tracking the current response to sinusoidal voltage inputs at various frequencies, we found that the  
413  $f_{res}$  and  $f_{\phi=0}$  are driven by the peak phase of  $I_{Ca}$ , and that  $f_{res}$  and  $f_{\phi=0}$  are nearly equal because of the  
414 phase matching of  $I_{Ca}$  with  $I_L$ . This is not always the case for neuronal models, and dynamical systems in

415 general, not even for linear models, except for the harmonic oscillator [18-20]. In fact, as we mentioned  
416 above, this is not the case for the  $I_{Ca}$  model used in [16], although our results on the  $I_{Ca}$  inactivation time  
417 constant are consistent with that study. In these models phase advance for low input frequencies  
418 required the presence of  $I_H$ . The underlying mechanisms are still under investigation and are beyond the  
419 scope of this paper. However, the fact that it occurs was crucial to develop a method to investigate the  
420 dependence of the resonant properties, particularly the dependence of the  $f_{res}$  on the  $I_{Ca}$  time constants,  
421 using phase information. To date, no other analytical method is available to understand the mechanisms  
422 underlying this type of phenomenon in voltage clamp. The tools we developed are applicable to other  
423 neuron types for which  $f_{res}$  is equal to or has a functional relationship with  $f_{\phi=0}$ . However, the conditions  
424 under which such a functional relationship exists still needs to be investigated.

425 Linear correlations between biophysical parameters of the same or different currents have been  
426 reported [37] and may be important in preserving the activity of the model neuron and its subthreshold  
427 impedance profile attributes [41]. Previous studies examined combinations of parameters in populations  
428 of multi-compartment conductance-based models fit to electrophysiological data [16, 51] and found  
429 only weak pairwise correlations suggesting that the correlations do not arise from electrophysiological  
430 constraints. In contrast, constraining the parameters of the ionic currents found to be essential for MPR  
431 in PD neuron by MPR attributes, we observed strong correlations underlying parameters when the  $Z$  and  
432  $\phi$  were constrained by the experimental data. We found that constraining the model parameters by  $f_{res}$   
433 produced a correlation between the values of time constants of  $I_{Ca}$  among the population of ~9000  
434 optimal parameter sets. Furthermore, running a 2D sensitivity analysis confirmed that the time  
435 constants were constrained so that the effect of making inactivation slower was compensated for by  
436 making activation faster to maintain  $f_{res}$  constant.

437 The optimal model parameter sets showed a nonlinear co-variation relationship between the  $\bar{g}_{Ca}$  and  
438 half-inactivation voltage of  $I_{Ca}$ . However, the models could be divided into two groups, low and high  
439  $\bar{g}_{Ca}$  in each of which this co-variation was close to linear. Interestingly, although  $I_{Ca}$  alone was the  
440 primary current underlying MPR, in the absence of  $I_H$  (with  $\bar{g}_H = 0$ ) the models were restricted to the  
441 high  $\bar{g}_{Ca}$  group. A 2D sensitivity analysis showed that co-varying parameters in each groups along their  
442 respective correlation lines preserved  $Q_z$  without affecting  $f_{res}$ , indicating that each group requires a  
443 distinct changes in one parameter to compensate for effects of changes in the other. Local sensitivity  
444 analysis showed that changes in  $V_{1/2}^{Ca^b}$  had opposite effects on  $f_{res}$  between high and low  $\bar{g}_{Ca}$  groups.

445 Increasing  $V_{1/2}^{Ca^h}$  decreased  $f_{res}$  in high  $\bar{g}_{Ca}$  models but increased it in low  $\bar{g}_{Ca}$  models. A previous  
446 modeling study has found that changes in  $V_{1/2}^{Ca^h}$  greatly influenced the amplitude of MPR with little effect  
447 on post-inhibitory rebound in thalamic neurons [21]. It would be interesting to verify whether the  
448 mechanisms that generate MPR overlap with those that contribute to post-inhibitory rebound  
449 properties.

450 Previous work in our lab has shown that the voltage range of oscillations significantly affects  $f_{res}$  [13].  
451 Here we show that decreasing,  $V_{low}$ , the lower bound of the oscillation voltage of the PD neuron, from -  
452 60 to -70 mV, significantly shifted  $f_{res}$  to smaller values without affecting  $Z_{max}$ . Within our optimal model  
453 parameter sets, we obtained a set of ~1000 models in the intermediate  $\bar{g}_{Ca}$  range that produced a  
454 similar shift in  $f_{res}$  but no change in  $Z_{max}$ . Because  $V_{low}$  greatly affects both  $I_{Ca}$  inactivation and  $I_H$   
455 activation, this indicated a potential interaction between these two currents. In fact, we found that  
456 because  $I_H$  and  $I_{Ca}$  are activated preferentially in different voltage ranges, their amplitudes needed to be  
457 balanced to keep  $Z_{max}$  unchanged when  $V_{low}$  was decreased. If the ratio of  $I_H$  to  $I_{Ca}$  amplitudes is incorrect,  
458 then  $Z$  will amplify (for high  $\bar{g}_{Ca}$  models) or attenuate (for low  $\bar{g}_{Ca}$  models). The intermediate  $\bar{g}_{Ca}$   
459 models also showed a stronger  $\tau_m^{Ca} - \tau_h^{Ca}$  correlation, which may be important in matching the phase of  
460  $I_{Ca}$  with that of  $I_L$ . This group also showed a strong  $\bar{g}_H - \bar{g}_{Ca}$  correlation, which may provide a mechanism  
461 for controlling the changes in  $I_H$  amplitude at more negative voltage with similar changes in  $I_{Ca}$  amplitude  
462 at more positive voltages.

463 In contrast to the findings of Rathour and Narayanan [16], in our optimal models the  $I_H$  amplitude was  
464 not different across the groups with different  $I_{Ca}$  properties. However, since  $I_{Ca}$  and  $I_H$  are differentially  
465 modulated [45, 52], their functional role may overlap when their voltage thresholds and time constants  
466 are shifted by neuromodulation. Therefore, we expect that under certain neuromodulatory contexts,  $I_H$   
467 may play more of an active role in the generation of MPR. A similar effect of two ionic currents on  
468 resonance has been observed in the hippocampal pyramidal cells that participate in the theta rhythm, in  
469 which two currents, the slow potassium M-current and  $I_H$ , were found to operate at the depolarized and  
470 hyperpolarized membrane potentials respectively to generate theta-resonance [2].

471 In general, variability of ionic current expression in any specific neuron type should lead to great  
472 variability in network output. Yet, network output in general, and specifically the output of the  
473 crustacean pyloric network is remarkably stable across animals [30, 53, 54]. Our results suggest that in

474 oscillatory networks the interaction among ionic currents in an individual neuron may be tuned in a way  
475 that the variability of the output is reduced in response to oscillatory inputs. Although our  
476 computational study may provide some insight into how such stability is achieved, it also indicates a  
477 need for additional mathematical analysis to elucidate the underlying mechanisms.

478

## 479 **Methods**

### 480 **Electrophysiology**

481 The stomatogastric nervous system of adult male crabs (*Cancer borealis*) was dissected using standard  
482 protocols as in previous studies [14]. After dissection, the entire nervous system including the  
483 commissural ganglia, the esophageal ganglion, the stomatogastric ganglion (STG) and the nerves  
484 connecting these ganglia, and motor nerves were pinned down in a 100mm Petri dish coated with clear  
485 silicone gel, Sylgard 186 (Dow Corning). The STG was desheathed to expose the PD neurons for  
486 impalement. During the experiment, the dish was perfused with fresh crab saline maintained at 10-  
487 13°C. After impalement with sharp electrodes, the PD neuron was identified by matching intracellular  
488 voltage activity with extracellular action potentials on the motor nerves. After identifying the PD neuron  
489 with the first electrode, a second electrode was used to impale the same neuron in preparation for two-  
490 electrode voltage clamp. Voltage clamp experiments were done in the presence of  $10^{-7}$  M tetrodotoxin  
491 (TTX; Biotium) superfusion to remove the neuromodulatory inputs from central projection neurons  
492 (decentralization) and to stop spiking activity [13, 14].

493 Intracellular electrodes were prepared by using the Flaming-Brown micropipette puller (P97; Sutter  
494 Instruments) and filled with 0.6M K<sub>2</sub>SO<sub>4</sub> and 0.02M KCl. For the microelectrode used for current  
495 injection and voltage recording, the resistance was, respectively, 10-15MΩ and 25-35MΩ. Extracellular  
496 recording from the motor nerves was carried out using a differential AC amplifier model 1700 (A-M  
497 Systems) and intracellular recordings were done with an Axoclamp 2B amplifier (Molecular Devices).

### 498 **Measuring the Z-profile**

499 During their ongoing activity, the PD neurons produce bursting oscillations with a frequency of ~1 Hz  
500 and slow-wave activity in the range of -60 to -30 mV. Activity in the PD neuron is abolished by

501 decentralization. The decentralized PD neuron shows MPR in response to ZAP current injection when  
502 the current drives the PD membrane voltage to oscillate between -60mV and -30mV, which is similar to  
503 the slow-wave oscillation amplitude during ongoing activity [12]. The MPR profiles are not significantly  
504 different when measured in current clamp and voltage clamp [14]. Since the MPR depends on the  
505 dynamics of voltage-gated ionic currents, it will also depend on the range and shape of the voltage  
506 oscillation. Therefore, to examine how  $Z(f)$  in a given voltage range constrains the properties of voltage-  
507 gated currents and how factors that affect the voltage range change MPR, we measured  $Z(f)$  in voltage  
508 clamp [10].

509 To measure the Z-profile, the PD neuron was voltage clamped with a sweeping-frequency sinusoidal  
510 impedance amplitude profile (ZAP) function [55] and the injected current was measured [14]. To  
511 increase the sampling duration of lower frequencies as compared to the larger ones, a logarithmic ZAP  
512 function was used:

$$513 \quad ZAP(t) = v_0 + v_1 \sin(2\pi F(t)); \quad F(t) = f_{lo} t \left( \frac{f_{hi}}{f_{lo}} \right)^{t/T}.$$

514 The amplitude of the ZAP function was adjusted to range between -60 and -30 mV ( $v_0=-45$  mV,  $v_1=15$   
515 mV) and the waveform ranged through frequencies of  $f_{lo}=0.1$  to  $f_{hi}=4$  Hz over a total duration  $T=100$  s.  
516 Each ZAP waveform was preceded by three cycles of sinusoidal input at  $f_{lo}$  which smoothly transitioned  
517 into the ZAP waveform. The total waveform duration was therefore 130 s.

518 Impedance is a complex number consisting of amplitude and phase. To measure impedance amplitude,  
519 we calculated the ratio of the voltage and current amplitudes as a function of frequency and henceforth  
520 impedance amplitude will be referred to as  $Z(f)$ . To measure  $\varphi_Z(f)$ , we measured the time difference  
521 between the peaks of the voltage clamp ZAP and the measured clamp current. One can also measure  
522  $Z(f)$  by taking the ratio of the Fourier transforms of voltage and current. However, spectral leakage,  
523 caused by taking the FFT of the ZAP function and the nonlinear response, often resulted in a low signal-  
524 to-noise ratio and therefore in inaccurate estimates of impedance. Such cases would lead to less  
525 accurate polynomial fits compared to the cycle-to-cycle method described above and we therefore  
526 limited our analysis to the cycle-to-cycle method.

527 Because the average Z-profile may not be a realistic representation of a biological neuron, we used the  
528 attributes of  $Z$  and  $\phi$  measurements from a single PD neuron as our target. We characterized attributes

529 of  $Z$  into five objective functions used for fitting by specifying five points of the profile (fig 1a). These five  
530 points were:

- 531 •  $(f_0, Z_0)$ , where  $Z_0 = Z(f_0)$  and  $f_0 = 0.1$  Hz,  
532 •  $(f_{res}, Z_{max})$ , thereby capturing  $Qz = Z_{max} - Z_0$ ,  
533 •  $(f_1, Z(f_1))$  where  $f_1 = 4$  Hz,  
534 • The two frequencies at which  $Z = Z_0 + Q_z / 2$ . Pinning the profile to these points captures the frequency  
535 bandwidth  $\Lambda_{1/2}$  which is the frequency range for which  $f > Z_0 + Q_z / 2$  (fig 1a).

536 We also constructed five objective functions to capture the attributes of  $\varphi(f)$  at five points (fig 1b):

- 537 •  $(f_0, \varphi(f_0))$ ,  
538 •  $(f_{\varphi=0}, 0)$ , where  $f_{\varphi=0}$  is the phasonant frequency  
539 •  $(f_{\varphi_{max}}, \varphi_{max})$  where  $\varphi_{max}$  is the maximum phase advance,  
540 •  $(f_{\varphi_{min}}, \varphi_{min})$  where  $\varphi_{min}$  is the maximum phase delay,  
541 •  $(2$  Hz,  $\varphi_{f=2})$  capturing the phase at 2Hz.

542

### 543 Single-compartment model

544 We used a single-compartment biophysical conductance-based model containing only those currents  
545 implicated in shaping  $Z$  and  $\varphi$  [12]. We performed simulations in voltage clamp and measured the  
546 current as:

547 
$$I_{clamp} = I_{Cm} + I_L + I_{Ca} + I_H$$

548 where  $I_{Cm}$  is the capacitive current ( $C \frac{dV}{dt}$  in nA),  $C_m$  is set to 1 nF and  $I_L$  is the voltage-independent leak  
549 current in nA. The voltage-dependent currents  $I_{curr}$  ( $I_{Ca}$  or  $I_H$ ) in nA are given by

550 
$$I_{curr} = \bar{g}_{curr} m_{curr}^p h_{curr}^q (V - E_{curr})$$

551 where  $V$  is the ZAP voltage input (see below),  $m_{curr}$  is the activation gating variable,  $h_{curr}$  is the  
552 inactivation gating variable,  $\bar{g}_{curr}$  is the maximal conductance in  $\mu$ S,  $E_{curr}$  is the reversal potential in mV,

553 and  $p$  and  $q$  are non-negative integers. For  $I_{Ca}$ ,  $p = 3$ ,  $q = 1$  and, for  $I_H$ ,  $p = 1$  and  $q = 0$ . The generic  
554 equation that governs the dynamics of the gating variables is:

555

$$\frac{dx}{dt} = \frac{1}{\tau_x} (x_\infty(V) - x)$$

556 where  $x = m_{curr}$  or  $h_{curr}$ , and

557

$$x_\infty(V) = 1 / [1 + \exp((V - V_x)/k_x)]$$

558 The sign of the slope factor ( $k_x$ ) determines whether the sigmoid is an increasing (negative) or  
559 decreasing (positive) function of  $V$ , and  $V_x$  is the midpoint of the sigmoid.

560 A total of 8 free model parameters were defined (Table 1), which were optimized in light of the  
561 objective functions introduced above, to yield a good fit to the Z-profile attributes as described below.

562 The slope factors  $k_x$  of the sigmoid functions  $m_\infty^{Ca}(V)$ ,  $h_\infty^{Ca}(V)$ , and  $m_\infty^H(V)$  were fixed at -8 mV, 6 mV, and -7  
563 mV, respectively.  $V_{1/2}^{H_m}$  was fixed at -70 mV, using data from experimental measurements in crab [44].

564 The voltage-dependent time constant for  $I_H$  was also taken from [44] to be

565

$$\tau_m^H / [1 + \exp((V + 110) / -13)]$$

566 where the range of  $\tau_m^H$  is given in Table 1.

567

## 568 Fitting models to experimental Data

569 Computational neuroscience optimization problems have used a number of methods, such as the “brute-force”  
570 exploration of the parameter space [51] and genetic algorithms [56]. However, the brute-force method is  
571 computationally prohibitive for an 8-dimensional model parameter space, which would require potentially very  
572 fine sampling to find optimal models. [57]. We used an MOEA (evolutionary optimization) to identify optimal sets  
573 of model parameters constrained by experimental  $Z$  and  $\varphi$  attributes. MOEAs are computationally efficient at  
574 handling high-dimensional parameter spaces and other studies have used them to search for parameters  
575 constrained by other types of electrophysiological activity [57]

576 Evolutionary optimization finds solutions by minimizing a set of functions called objective functions, or simply  
577 objectives, subject to certain constraints. In our problem, each objective represents the Euclidean distance  
578 between the target and the model attributes of  $Z$  and  $\varphi$ . When optimizing multiple (potentially conflicting)  
579 objectives, MOEA will find a set of solutions that constitute trade-offs in objective scores. For instance, an optimal  
580 parameter set may include solutions that are optimal in  $f_{\text{res}}$  but not in  $Q_z$  or vice versa and a range of solutions in  
581 between that result from the trade-offs in both objectives. In this paper, we used the non-dominated sorting  
582 genetic algorithm II (NSGA-II) [38, 58] to find optimal solutions, which utilizes concepts of non-dominance and  
583 elitism, shown to be critical in solving multi-objective optimization problems [58]. Solution  $x_1$  is said to dominate  
584 solution  $x_2$  if it is closer to the target  $Z(f)$  and  $\varphi(f)$  profiles in at least one attribute (e.g.,  $f_{\text{res}}$ ) and is no worse in any  
585 other attributes (e.g.,  $Q_z$ ,  $Z_0$ , etc.).

586 NSGA-II begins with a population of 100 parameter combinations created at random within pre-determined lower  
587 and upper limits (Table 1). The objective values for each parameter combination are calculated and ordered  
588 according to dominance. First, the highest rank is assigned to all of the non-dominated, trade-off solutions. From  
589 the remaining set of parameters, NSGA-II selects the second set of trade-off solutions. This process continues  
590 until there are no more parameter combinations to rank. Genetic operators such as binary tournament selection,  
591 crossover, and mutation form a child population. A combination of the parent and child parameter sets form the  
592 population used in the next generation of NSGA-II [38, 58]. NSGA-II favors those parameter combinations—among  
593 solutions non-dominating with respect to one another—that come from less crowded parts of the parameter  
594 search space (i.e., with fewer similar, in the sense of fitness function values, solutions), thus increasing the  
595 diversity of the population. The crowding distance metric is used to promote large spread in the solution space  
596 [38].

597 We ran NSGA-II multiple times (3-5 times, until the mean values of the distributions of optimal  
598 parameters was stable) each time for 200 generations with a population size of 100, and pooled the  
599 solutions at the end of each run to form a combined population of ~9000 parameter combinations. The  
600 algorithm stopped when no additional distinct parameter combinations were found. The  $Z$  and  $\varphi$  values  
601 associated with the optimal parameter sets match the target features (objectives) defining  $Z$  and  $\varphi$  to  
602 within 5% accuracy.

603 To test whether two parameters were significantly correlated in the population of 9000 PD models, we  
604 calculated the Pearson's correlation coefficients for each pair of parameters and used a permutation  
605 test to determine the number of times the calculated correlation coefficient (using a random subset of  
606 20 models). The p-value was given as the fraction of R-values for the permuted vectors greater than the  
607 R-value for the original data [51]. We also used a t-test to determine whether the calculated slope of the

608 linear fit differed significantly from zero, which gave us identical results. We repeated both procedures  
609 2000 times, each time with a random subset of 20 models and calculated the percentage of times we  
610 obtained a p-value < 0.01.

611

## 612 Sensitivity Analysis

613 We assessed how the values of  $f_{\text{res}}$  and  $Q_z$  depend on changes in parameter values by performing a  
614 sensitivity analysis as in [59]. We split the model parameters into two categories: additive, for the  
615 voltage-midpoints of activation and inactivation functions, and multiplicative, for the maximal  
616 conductances and time constants. We changed the parameters one at a time and fit the relative change  
617 in the resonance attributes as a linear function of the relative parameter change. We changed the  
618 multiplicative parameters on a logarithmic scale to characterize parameters with both low and high  
619 sensitivity.

620 Multiplicative parameters were varied as  $p_{n+1} = \exp(\pm \Delta p_n) p_0$  with  $\Delta p_n = 0.001 * 1.15^n$  and the sign  
621 indicating whether the parameter was increased or decreased. To ensure approximate linearity, we  
622 added points to the fit until the  $R^2$  value fell below 0.98. The sensitivity was defined as the slope of this  
623 linear fit (fig 2). For example, if a resonance attribute has a sensitivity of 1 to a parameter, then a 2-fold  
624 change in the parameter results in a 2-fold change in the attribute. We changed additive parameters by  
625  $\pm 0.5$  mV.

626 We assessed the sensitivity of  $f_{\text{res}}$  and  $Q_z$  to parameter pairs ( $p_1$  and  $p_2$ ) that were correlated. We first fit  
627 a line through the correlated values in the  $p_1$ - $p_2$  space. We then shifted this line to pass through a subset  
628 of 50 random points in  $p_1$ - $p_2$  space, resulting in a family of parallel lines,  $L$ . For each point, we also  
629 produced a line perpendicular to a line  $L^\perp$ . For each model, we performed a sensitivity analysis as before  
630 but used the linear fit equation  $L$  or  $L^\perp$  to calculate value of  $p_2$ . We fit the relative change in the  $Z(f)$   
631 attribute as a linear function of the correlated change in  $p_1$  and  $p_2$ . We used the slope of the linear fit to  
632 represent the sensitivity. We used a 2-and 3-way repeated measures ANOVA and the lsmeans function  
633 in R to perform pairwise comparisons of means in testing for significant differences between each group  
634 of  $g_{\text{Ca}}$ , each direction,  $L$  and  $L^\perp$ , and between each  $Z$  attribute,  $f_{\text{res}}$  and  $Q_z$ .

635 For each model, we solved a system of three differential equations for  $m_H$ ,  $m_{Ca}$  and  $h_{Ca}$  (voltage was  
636 clamped). All simulations were performed using the modified Euler method [60] with a time step of 0.2  
637 ms. The simulation code, impedance calculations, and MOEA were written in C++. MATLAB (The  
638 MathWorks) and R were used to perform statistical analyses.

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817

## 818 Supporting Information Legends

819 **S1. Changing the value of  $V_{1/2}^{H_m}$  does not change the correlations observed among the model**

820 **parameters. a.** Correlations shown in Fig. 8b with  $V_{1/2}^{H_m}$  at -70 mV. **b.** Correlations obtained with  $V_{1/2}^{H_m}$  set  
821 to -96 mV (red dots). MOEA was run only once in this case, compared to 5 times in panel a (hence the  
822 difference in the number of points). Black dots are the same as panel **a**. Note that the values of  $\bar{g}_H$  in  
823 this case are about 10 times larger than those in panel **a**, but the correlations (green boxes) remain  
824 intact. More importantly, the range of parameters other than  $\bar{g}_H$  is exactly the same in both cases.

825 **S2.  $I_H$  extends the dynamic range of  $I_{Ca}$  parameters over which  $I_{Ca}$ -mediated MPR occurs.** Parameter  
826 values for the optimal models in  $\bar{g}_{Ca}$  -  $V_{1/2}^{Ca_h}$  space shown for all models (grey dots) and those without  $I_H$   
827 (blue dots). We removed  $I_H$  by setting  $\bar{g}_H = 0$ , and ran the MOEA multiple times using the same Z- and  
828  $\varphi$ -profiles to constrain the  $I_{Ca}$  parameters. A linear fit (green) shows that, when  $\bar{g}_H = 0$ , the relationship  
829 between  $\bar{g}_{Ca}$  -  $V_{1/2}^{Ca_h}$  is linear and matches a narrow range of the high  $\bar{g}_{Ca}$  values in fig 8c.

## 830 Figure Legends

831 **Fig 1. Characterization of impedance amplitude  $Z(f)$  and phase  $\varphi(f)$  into target objective functions was**  
832 **performed to constrain the model parameters.** The individual objective functions which collectively  
833 measure goodness-of-fit were taken as the distance away from characteristic points along the  $Z(f)$  and  
834  $\varphi(f)$  profiles (green circles). **a.** The attributes used along  $Z(f)$  were  $Z_0=Z(f_0)$  at  $f_0=0.1$  Hz,  $Z(f_1)$  at  $f_1 = 4$  Hz,  
835 maximum impedance  $Z_{max}=Z(f_{res})$  and the two points of the profile at  $Z_0+Q_Z/2$ .  $Q_Z=Z_{max}-Z_0$ .  $\Lambda_{1/2}$  is the width  
836 of the profile at  $Z_0+Q_Z/2$ . **b.** The attributes used along  $\varphi(f)$  were  $\varphi(f_0)$ , maximum advance  $\varphi_{max}$ , zero-  
837 phase frequency  $f_{\varphi=0}$ ,  $\varphi_{f=2}$  at 2 Hz and maximum delay  $\varphi_{min}$ .

838 **Fig 2. Linear fits used to assess the sensitivity of impedance attributes on changes in parameters.** Each  
839 model parameter was changed from the optimal value (origin) in both directions on a logarithmic scale  
840 to characterize parameter sensitivity. The slope of a linear fit of the relative change in the  $Z(f)$  attribute  
841 and the parameter was measured as sensitivity. The parameter was changed until the fit was no longer  
842 linear ( $R^2 < 0.98$ ).

843 **Fig 3. Membrane potential resonance MPR of the PD neuron was measured in voltage clamp.** **a.** During  
844 ongoing activity, the PD neuron shows a slow-wave voltage waveform ranging approximately between -

845 60 and -30 mV. **b.** The membrane potential ( $V_{\text{zap}}$ ) and the injected current ( $I_{\text{PD}}$ ) were recorded when the  
846 PD neuron was voltage-clamped using a ZAP function between -60 and -30mV and sweeping frequencies  
847 between 0.1 and 4 Hz. The arrowhead indicates resonance, where the current amplitude is minimal and  
848  $Z$  is maximal. **c.** The impedance amplitude  $Z(f)$  (**c1**) and phase  $\varphi(f)$  (**c2**) profiles of the PD neuron  
849 recorded in 18 preparations. The cross bars show the mean and SEM of  $f_{\text{res}}$  and  $Z_{\text{max}}$  (**c1**) and  $f_{\varphi=0}$  (**c2**).  
850 The shaded region indicates the 95% confidence interval. **d.** The range of three  $Z(f)$  attributes  $f_{\text{res}}$ ,  $Q_Z$ , and  
851  $\Lambda_{1/2}$  and one  $\varphi(f)$  attribute  $f_{\varphi=0}$ . Each attribute was normalized to the median of its distribution for cross  
852 comparison. CoV is the coefficient of variation.

853 **Fig. 4. Optimal models were fit to the impedance attributes of a single PD neuron.** The  $Z(f)$  (**a**) and  $\varphi(f)$   
854 (**b**) profiles of 500 randomly selected models from the optimal dataset (light blue curves) are compared  
855 to the target neuron's impedance profiles (red circles). All attributes (except  $\varphi_{\text{max}}$ ) were captured to  
856 within 5% accuracy. The values of the biological target impedance amplitude attributes (in Hz, MΩ)  
857 were:  $(f_0, Z_0) = (0.1, 8.2)$ ,  $(f_{\text{res}}, Z_{\text{max}}) = (1, 13.7), (0.4, 11.65), (2.5, 11.65)$  and  $(4, 9.6)$ . The target  
858 impedance phase attributes (in Hz, rad) were:  $(0.1, 0)$ ,  $(f_{\varphi_{\text{max}}}, \varphi_{\text{max}}) = (0.4, 0.5)$ ,  $(f_{\varphi=0}, 0) = (1.05, 0)$ ,  $(2, -4)$ ,  
859  $(f_{\varphi_{\text{min}}}, \varphi_{\text{min}}) = (4, -0.4)$ .

860 **Fig 5. Passive and voltage-gated currents contribute to the generation of MPR.** **a.**  $Z(f)$  for a random  
861 model from the optimal dataset. We measured the steady-state response to sinusoidal voltage inputs  
862 (inset) at 0.1 Hz,  $f_{\text{res}}=1$  Hz, and 4 Hz. Voltage-gated ( $I_{\text{Ca}}$  and  $I_{\text{H}}$ ) and passive currents ( $I_{\text{L}} + I_{\text{Cm}}$ ) are plotted as  
863 a function of voltage (left) and normalized time or cycle phase (right) at 0.1 Hz (**b**), 1 Hz (**c**), and 4Hz (**d**).  
864 The inset in **5c** shows one standard deviation around the mean for the data shown in the right panel,  
865 calculated for 200 randomly selected models.

866 **Fig 6.  $f_{\text{res}}$  and  $f_{\varphi=0}$  of the optimal models are nearly identical.** **a.**  $Z(f)$  (top) and  $\varphi(f)$  (bottom) for a  
867 representative optimal model. Green dots indicate  $f_{\text{res}}$  (top) and  $f_{\varphi=0}$  (bottom). **b.** Histogram showing the  
868 difference between  $f_{\text{res}}$  and  $f_{\varphi=0}$  for 500 randomly selected models. A comparison of  $f_{\text{res}}$  and  $f_{\varphi=0}$  of the  
869 experimental data of the PD neuron shows a similar distribution (inset, N=18). **(c)** Plots of steady-state  
870 responses of  $I_{\text{Ca}}$ ,  $I_{\text{L}}$ , and  $I_{\text{total}}$  to sinusoidal voltage inputs at the frequencies marked in panel **a** shown as a  
871 function of normalized time (cycle phase). Dotted vertical line indicates cycle phase 0.5 where the  
872 passive currents peak. Solid lines connect the minimum of  $I_{\text{Ca}}$  to the peak of  $I_{\text{total}}$ . The two lines nearly  
873 align at  $f_{\varphi=0}$ .

874 **Fig 7. The time constants of  $I_{Ca}$  activation and inactivation control  $f_{res}$  and  $Z_{max}$ .** The  $Z(f)$  profiles are  
875 plotted for a randomly selected optimal model (green) at different values of  $\tau_m^{Ca}$  (**a**) and  $\tau_h^{Ca}$  (**b**). Note  
876 that  $f_{res}$  of the control (100%) values are at 1 Hz (dashed vertical line). The currents  $I_{Ca}$ ,  $I_L$  and  $I_{total}$  plotted  
877 as a function of cycle phase at 50% (**c1, d1**), 100% (**c2, d2**), and 150% (**c3, d3**) of the control values of  $\tau_m^{Ca}$   
878 (**c**) and  $\tau_h^{Ca}$  (**d**). In each panel of c and d, the currents are shown at 1 Hz (along the dashed lines in **a, b**)  
879 and at  $f_{res}$  (filled circles in **a, b**).

880 **Fig 8. The optimal models show variability in individual and pairs of parameters.** **a.** The range of  
881 parameters for all optimal models (~9000). Each parameter is normalized by its median value for cross  
882 comparison. The median values were  $\bar{g}_L = 0.096\mu S$ ,  $\bar{g}_H = 0.164\mu S$ ,  $\bar{g}_{Ca} = 0.172\mu S$ ,  $\tau_m^h = 2179ms$ ,  $V_{1/2}^{Ca_m} = -51mV$ ,  
883  $\tau_m^{Ca} = 70ms$ ,  $V_{1/2}^{Ca_h} = -67mV$ ,  $\tau_h^{Ca} = 458ms$ . Three representative optimal model parameter sets are shown  
884 (cyan, orange, purple solid line segments) indicating that widely different parameter combinations can  
885 produce the biological  $Z(f)$  and  $\varphi(f)$ . CoV is coefficient of variation. **b.** Pairwise relationships among  
886 parameters of all optimal models (black dots). The range of parameter space was sampled within the  
887 prescribed limits given to the optimization routine, shown by including the sampled non-optimal models  
888 (grey). Permutation test showed significant pairwise correlations (green highlighted boxes with linear  
889 fits shown as green lines). **c.** Optimal models could be separated into two highly significant linear fits  
890 (green lines) in  $\bar{g}_{Ca}$  -  $V_{1/2}^{Ca_h}$  according to whether  $\bar{g}_{Ca} < 0.05$  (red; Low  $\bar{g}_{Ca}$ ) or  $\bar{g}_{Ca} > 0.05$  (cyan; High  $\bar{g}_{Ca}$ ). **d.**  
891 All pairwise relationships, separated on the low or high  $\bar{g}_{Ca}$  (colors as in panel **c**). Green boxes are the  
892 same as in **b**.

893 **Fig 9. The effect of the lower voltage bound  $V_{low}$  of oscillations on  $f_{res}$  and  $Z_{max}$  constrains the optimal models.** **a.**  
894 An example of the change in  $Z(f)$  measured in the biological PD neuron for  $V_{low} = -60mV$  (black line) and  $V_{low} = -70mV$   
895 (grey line). Inset shows the bounds of voltage clamp inputs in the two cases. **b.** Shifting  $V_{low}$  from -60 mV to -70 mV  
896 lowers the value of  $f_{res}$  measured in the PD neuron significantly, without influencing  $Z_{max}$  (**b. Experimental**).  $f_{res}$  and  
897  $Z_{max}$  values measured in a random subset of optimal model neurons corresponding to low or high  $\bar{g}_{Ca}$  values  
898 produced the same  $f_{res}$  and  $Z_{max}$  values at  $V_{low} = -60mV$  (black dots), but distinct  $f_{res}$  and  $Z_{max}$  values at  $V_{low} = -70mV$   
899 (low  $\bar{g}_{Ca}$ : red dots; high  $\bar{g}_{Ca}$ : cyan dots). A subset of optimal models could reproduce the experimental result in  
900 which  $f_{res}$  shifted to significantly lower values without affecting  $Z_{max}$ . (grey dots). **(c)**  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  relationship  
901 separating out the different groups of models producing different responses to changes in  $V_{low}$  (colors correspond  
902 to **b** Model panel). Models depicted by grey dots are referred to as intermediate  $\bar{g}_{Ca}$  models. (**d1-e3**) mean  
903 voltage-gated ionic currents  $I_{Ca}$ ,  $I_H$  and  $I_{Ca}+I_H$  and  $I_{total}$ , shown as a function of voltage for  $V_{low} = -60$  mV (**d1-d3**) and

904  $V_{\text{low}} = -70 \text{ mV}$  (**e1-e3**). Numbers correspond to the location along the  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  as shown in **c. f.** The intermediate  
905  $\bar{g}_{Ca}$  models (grey dots) show a distinct  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  linear correlation. **g.** Intermediate  $\bar{g}_{Ca}$  models (grey dots) show a  
906 distinct and tighter  $\tau_m^{Ca} - \tau_h^{Ca}$  correlation compared to all optimal models (black dots). **h.** Intermediate  $\bar{g}_{Ca}$  models  
907 (grey dots) show a strong  $\bar{g}_{Ca} - \bar{g}_H$  linear correlation that is not observed for all optimal models (black dots).

908 **Fig 10. Assessing the dependence of  $f_{res}$  and  $Q_z$  on the  $\tau_m^{Ca} - \tau_h^{Ca}$  linear correlation.** **a.** Parameter values for each  
909 model were changed along a line parallel (, blue) to the correlation line (black) or along a perpendicular line ( $\perp$ ,  
910 grey). This was done for models with high (cyan; **a1**), low (red; **a2**) and intermediate (grey; **a3**)  $\bar{g}_{Ca}$  models. For  
911 each model and each line, or  $\perp$ , we fit a line to the relative change in either  $f_{res}$  or  $Q_z$  as a function of the relative  
912 change in  $\bar{g}_{Ca}$ . **b.** The sensitivity values of  $f_{res}$  or  $Q_z$  to or  $\perp$  are shown for the three groups. **c.** Impedance profiles  
913 showing how  $Q_z$  changes when the parameters vary along a line parallel (blue) or perpendicular (grey) to the  
914  $\tau_m^{Ca} - \tau_h^{Ca}$  correlation line in one optimal model. Arrows show the direction of the movement of  $Z_{\max}$  and  $f_{res}$  for the  
915 change in parameters along or  $\perp$  for the high (**c1**), low (**c2**) and intermediate (**c3**)  $\bar{g}_{Ca}$  model.

916 **Fig 11. Assessing the dependence of  $f_{res}$  and  $Q_z$  on the linear  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  correlation.** **a.** Parameter values for  
917 each model were changed along a line parallel (, blue) to the correlation line (black) or along a perpendicular line  
918 ( $\perp$ , grey). This was done for models with high (cyan; **a1**), low (red; **a2**) and intermediate (grey; **a3**)  $\bar{g}_{Ca}$  models.  
919 For each model and each line, or  $\perp$ , we fit a line to the relative change in either  $f_{res}$  or  $Q_z$  as a function of the  
920 relative change in  $\bar{g}_{Ca}$ . **b.** The sensitivity values of  $f_{res}$  or  $Q_z$  to or  $\perp$  are shown for the three groups. **c.** Impedance  
921 profiles showing how  $Q_z$  changes when the parameters vary along a line parallel (blue) or perpendicular (grey) to  
922 the  $\bar{g}_{Ca} - V_{1/2}^{Ca_h}$  correlation line in one optimal model. Arrows show the direction of the movement of  $Z_{\max}$  and  $f_{res}$   
923 for the change in parameters along or  $\perp$  for the high (**c1**), low (**c2**) and intermediate (**c3**)  $\bar{g}_{Ca}$  model.

924 **Fig 12. Assessing the dependence of  $f_{res}$  and  $Q_z$  of the intermediate  $\bar{g}_{Ca}$  models on the linear  $\bar{g}_{Ca} - \bar{g}_H$**   
925 **correlation.** **a.** Parameter values for each model were in the intermediate  $\bar{g}_{Ca}$  group (see fig 9) were changed  
926 along a line parallel (, blue) to the correlation line (black) or along a perpendicular line ( $\perp$ , grey). For each model  
927 and each line, or  $\perp$ , we fit a line to the relative change in either  $f_{res}$  or  $Q_z$  as a function of the relative change in  
928  $\bar{g}_{Ca}$ . **b.** The sensitivity values of  $f_{res}$  or  $Q_z$  to or  $\perp$  are shown for the three groups. **c.** Impedance profiles showing  
929 how  $Q_z$  changes when the parameters vary along a line parallel (blue) or perpendicular (grey) to the  $\bar{g}_{Ca} - \bar{g}_H$   
930 correlation line in one optimal model. Arrows show the direction of the movement of  $Z_{\max}$  and  $f_{res}$  for the change in  
931 parameters along or  $\perp$ .

932 **Tables**

	$\bar{g}_L$	$\bar{g}_H$	$\bar{g}_{Ca}$	$\tau_m^H$	$V_{I/2}^{Ca_{\infty}^m}$	$\tau_m^{Ca}$	$V_{I/2}^{Ca_{\infty}^h}$	$\tau_h^{Ca}$
Low	0	0	0	0	-75	0	-75	0
High	0.15	0.35	0.35	3000	-30	100	-30	1000

**Table 1.** Limits of parameter values allowed for the PD neuron models.  $V_{I/2}^{Ca_{\infty}^m}$  was fixed at -70 mV since there is little variability in the reporting of this experimental measurement [45, 61]. Voltages are in mV, maximal conductances in  $\mu$ S and time constants in ms.

933

	$\bar{g}_L$	$\bar{g}_H$	$\bar{g}_{Ca}$	$\tau_m^H$	$V_{I/2}^{Ca_{\infty}^m}$	$\tau_m^{Ca}$	$V_{I/2}^{Ca_{\infty}^h}$	$\tau_h^{Ca}$
$\bar{g}_L$		<u>0.003</u>		0.358	0.147	0.272	<u>0.002</u>	0.347
$\bar{g}_H$	<u>0.003</u>			0.288	<u>0.03</u>	0.442	0.104	0.21
$\bar{g}_{Ca}$	0.349	0.046		0.449	0.512	0.485	<u>&lt;0.001</u>	0.129
$\tau_m^H$	0.054	<u>0.001</u>	0.002		0.349	0.470	0.417	0.121
$V_{I/2}^{Ca_{\infty}^m}$	0.233	0.496	0.138	0.277		0.378	0.452	0.037
$\tau_m^{Ca}$	0.133	0.510	0.191	0.253	0.05		0.318	<u>0.036</u>
$V_{I/2}^{Ca_{\infty}^h}$	0.368	0.07	<u>&lt;0.001</u>	<u>&lt;0.001</u>	0.068	0.092		0.27
$\tau_h^{Ca}$	0.307	0.452	<u>0.008</u>	0.05	<u>&lt;0.001</u>	<u>&lt;0.001</u>	<u>0.001</u>	

**Table 2.** Statistical p-values obtained using the permutation test of pairwise comparisons for low (lower triangle) and high (upper triangle)  $\bar{g}_{Ca}$ . Underlined values are statistically significant ( $p<0.05$ ).

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