A positive feedback at the cellular level promotes robustness and modulation at the circuit level

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Abstract

The paper highlights the role of a particular feedback mechanism at the cellular level in the robustness and modulation properties of oscillations at the circuit level. The results are presented in the context of half-center oscillators, which are simple rhythmic circuits composed of two inhibitory neuronal populations reciprocally connected. It is well known that such rhythms rely on a particular excitability property, the post-inhibitory rebound, to which two distinct ionic currents contribute, $I_h$ and $I_{CaT}$. The paper proposes that, beyond the excitability property in itself, its slow-positive feedback nature at the cellular level is fundamental for the robustness and modulation at the circuit level. Because $I_{CaT}$ is a source of slow-positive feedback but not $I_h$, this suggests a distinctive role of the calcium current involved in PIR mechanisms. This study thereby identifies an essential cellular property to be retained at the network level in modeling network robustness and modulation.

Author Summary

Biological rhythms play a major role in the functioning of the brain, both under physiological and pathological conditions. Control, regulation, and function of these rhythms have been widely studied, experimentally and computationally, but much awaits to be discovered. The main message of this paper is to highlight the role of a key excitability property at the cellular level in endowing oscillations with robustness and modulation properties at the network level. Robustness of the oscillations yields a stable behavior unaffected by variability and noise, whereas modulation provides the ability to adapt to a changing environment. The results of the paper are presented on one of the simplest and most extensively studied network rhythms but the proposed mechanism is general.

Introduction

Biological rhythms play a major role in the functioning of the brain but much remains to be understood regarding their control, regulation, and function. In the last decades, many advances in this important question of neuroscience have come from the experimental and computational study of central pattern generators (CPGs), which endogenously produce precise rhythmic inputs directly related to specific motor cerebral functions.

The detailed experimental study of specific circuits such as the crab stomatogastric ganglion (STG) has revealed the richness of regulatory mechanisms that allow an organism to tightly control a specific rhythm at the circuit level, to sustain it in spite of broad variability at the component (cellular and molecular) level, and to adapt its frequency or phase properties to a changing environment.

This remarkable control is achieved by concurrent regulatory mechanisms that range across vastly different spatial and temporal scales, posing a significant complexity challenge. Experimental work should benefit from computational models that can assist and guide experimental studies but models at the...
circuit level usually rely on mathematical simplifications at the component level. The question of which details at the cellular level must be retained at the network level is largely open, especially when it comes to understand the robustness and the modulation capabilities of the network [7].

Motivated by this general question, we present in this paper a simple feedback mechanism at the cellular level that has a key influence on robustness and modulation at the circuit level. We illustrate this property via the computational study of the reciprocal-inhibition network, or half-center oscillator, an archetype model of CPG circuits: two homogenous neuronal populations that do not oscillate in isolation, but oscillate in an antiphasic rhythm when reciprocally connected by mutual inhibition [8–10]. Because of the widespread occurrence of this circuit motif in neuronal circuits, the intrinsic (cellular) and extrinsic (synaptic) mechanisms that generate the circuit oscillation have been extensively studied, both computationally and experimentally [9, 11, 12, 13]. A specific excitability property at the cellular level, the post-inhibitory rebound (PIR), is known to be a key cellular player of the circuit oscillation [9]. Furthermore, two specific ionic currents, \( I_h \) and \( I_{CaT} \), have long been identified as key ionic players of cellular PIR and are most often found in neurons participating in CPGs [16].

Previous studies have not attributed a fundamentally different role to those two ionic currents regarding their role in robustness and modulation at the circuit level. The novel contribution in this paper is to highlight that those two ionic currents nevertheless differ in at least one simple but fundamental aspect: both regulate the neuron excitability in a time-scale relevant for the network rhythm, but only one of them acts as a source of positive feedback in this time-scale. Together, they therefore regulate a balance of positive and negative feedback in one particular time-scale (the time-scale of calcium activation, of the order of 10ms) and one (cellular) spatial scale. The objective of the present paper is to demonstrate via a computational study that this particular feedback balance is fundamental for the robustness and modulation properties of the circuit level rhythm, and that the absence of the positive feedback in that particular spatiotemporal window is particularly detrimental both to robustness and modulation at the circuit level.

Our results predict that PIR per se is not a sufficient cellular excitability property to be retained in simplified computational models of the network when studying its robustness and modulation properties. In addition, its regenerative (positive feedback) or restorative (negative feedback) nature must be retained as an important regulatory parameter at the cellular level. We emphasized in previous work the importance of this balance at the cellular level in regulating bursting excitability [17] and its widespread regulation in different types of neurons [18]. The present paper can be seen as a continuation of this work, moving from the role of regenerativity at the cellular level to its importance at the circuit level.

**Results**

**Cellular PIR for network oscillations**

To assess the role of cellular properties in network rhythms, we consider one of the simplest and most studied networks: the *half-center oscillator*. The network rhythm results from the mutual inhibition (I) of two neurons that do not oscillate endogenously in isolation [8–10] (Figure 1, A). Half-center oscillators have been identified at the core of most endogenous rhythmic circuits, such as CPGs governing locomotion [8–11, 15] or respiration [1, 15, 19]. Oscillations in half-center oscillators are triggered by an external pulse of hyperpolarizing current (Figure 1, B). When released from hyperpolarization, the cell generates a burst-like transient depolarization with one or more spikes. This activity hyperpolarizes the other cell via the synaptic GABAergic connection which in turn triggers a transient burst. The cycle repeats leading to an antiphase rhythm between the two neurons. At the network level, this simple rhythm is characterized by a few simple quantities (Figure 1, B): the network—or interburst—frequency, \( f_{\text{network}} \) (in blue), reflecting the period of the network oscillation, the duty cycle, \( dc \) (in orange), which is the ratio between a burst duration and the time duration between two bursts \((1/f_{\text{network}})\), and the ratio \( r_{dc} \).
between the duty cycle in neuron 1 and in neuron 2 \( (dc_1/dc_2) \).

**Figure 1. Oscillations in I-I networks.** A: Reciprocal inhibitory-inhibitory (I-I) network. The two I cells are connected reciprocally with GABAergic synapses. B: Membrane potential of the two cells and applied current in the network. Definition of two network quantities: the network frequency in blue, and the duty cycle and duty cycle ratio in orange. The horizontal bar represents a 1s time period.

The transient depolarization following the termination of an hyperpolarizing input is an essential cellular property for the network rhythm, best known in the literature as post-inhibitory rebound (PIR) \[9\]. Two major ionic currents have been shown to influence the PIR: i) the hyperpolarization-activated cation current, \( I_h \), an hyperpolarization-activated inward current that contributes to rebound responses in a diverse array of neurons in invertebrates and vertebrates \[16\]; ii) the low-threshold T-type calcium current, \( I_{CaT} \), which is deinactivated by hyperpolarization and then activates upon release from inhibition \[20\]. While the two types of currents may cooperate to shape the properties of PIR, we emphasize a fundamental difference between the two: \( I_h \) provides a negative feedback at resting potential by generating an inward current that counteracts the external hyperpolarization, whereas \( I_{CaT} \) provides a positive feedback at resting potential by providing an inward current which is deinactivated by hyperpolarization and which then activates upon release from inhibition. In the terminology of \[18\], \( I_{CaT} \) is slow regenerative—that is, it is a source of positive feedback in the slow time-scale of its activation. Figure 2 reflects that the balance of positive and negative feedback in the slow time-scale vastly differs among different published PIR models depending on how \( I_{CaT} \) is modeled. The slow feedback is necessarily negative in the absence of \( I_{CaT} \) due to the potassic spike current \( I_{Kd} \), a slow-restorative current, but remains negative even in the presence of \( I_{CaT} \) when its activation is not slow enough to impact the excitability of the rhythm at the circuit level.

The balance between slow-restorative and slow-regenerative channels is important in that it controls the nature of PIR modulation. With purely negative feedback (restorative PIR), the control of PIR is exogenous as illustrated in Figure 3: the polarization level, an extrinsic parameter, and the PIR conductance parameter, an intrinsic property, modulate the first spike latency, the firing rate, and the PIR duration. In contrast, with positive feedback (regenerative PIR), the control of PIR is endogenous. Modulation of the polarization level or intrinsic conductance affects the PIR only slightly. Instead, modulation of the PIR is primarily achieved through variation of the intrinsic neuronal properties, that is, the balance between restorative and regenerative currents which smoothly shifts the PIR response between purely restorative and strongly regenerative. Variation of any neuron parameter that affects the balance between restorative and regenerative currents is an endogenous source of modulation of the PIR properties.

At the cellular level, the endogenous or exogenous behavior of the PIR has a minor impact on PIR traces and this distinction seems nonessential. However, we will see in the next sections that the endogenous nature of PIR is fundamental to robustness and modulation of the network rhythm.
Figure 2. The regenerative nature of the PIR. Regenerativity of the PIR is controlled by a balance between currents that provide slow-negative feedback (e.g. PIR with $I_h$, where $I_{Kd}$ is slow-restorative) and currents that provide slow-positive feedback (e.g. $I_{CaT}$). Models exhibit a varying degree of regenerativity. The current but also the way it is modeled sets the regenerativity of the PIR. Each row represents a different slow feedback: negative, weak positive, and strong positive. For each feedback, the current responsible for the PIR and one model in the literature are given in the second column. The third column represents the important time-scales and time constants of the model: the fast time-scale given by $\tau_{mNa}$, the slow time-scale given by $\tau_{mKd}$, and the ultra-slow time-scale given by $\tau_{Ca^{2+}}$. The PIR traces for each current are given in the fourth column. The horizontal bar represents a 1s time period.

Robustness of network oscillations requires regenerative PIR

There exists extensive experimental evidence that the rhythmic activity of neuronal circuits is robust against variability in intrinsic parameters (such as ionic conductances across neurons), extrinsic parameters (such as synaptic conductances), and exogenous noise (such as synaptic currents external to the circuit) [21-24]. We tested the robustness of half-center oscillators in a network with restorative PIR against a network with regenerative PIR. Our model contains one PIR current with distinct parameters to control its maximal conductance and its slow regenerativity (see methods). The results show the drastic influence of cellular slow regenerativity in the robustness of the network.

Variability in cellular properties

Intrinsic variability of the network was studied by varying the maximal conductance of the PIR current. Variability in the cellular properties dramatically impacts the oscillatory behavior of the network with restorative PIR (Figure 4 A-D). The network rhythm is significantly perturbed by 25% of variability and completely destroyed beyond 75% of variability. In sharp contrast to the restorative case, the network oscillations with regenerative PIR are robust against intrinsic variability up to 200% (Figure 4 E-H). Remarkably, the network frequency is almost unaffected by the intrinsic variability, a consequence of the endogenous nature of PIR with regenerative currents. Instead, the network frequency is strongly affected by intrinsic variability with restorative currents, a consequence of the exogenous nature of restorative
Figure 3. Exogenous versus endogenous behavior of the PIR. Restorative currents make the PIR exogenous, i.e. sensitive to a variation of extrinsic (45% decrease in first spike latency, 129% increase in firing frequency at the burst onset, and 733% increase in PIR length) and intrinsic parameters (24% decrease in first spike latency, 82% increase in firing frequency at the burst onset, and 182% increase in PIR length). Regenerative currents make the PIR endogenous, i.e. insensitive to a variation of conductance parameters (20% decrease in first spike latency in both cases, 11% and 14% increase in firing frequency at the burst onset, and 81% and 70% increase in PIR length).

PIR.

Variability in network properties

The robustness of the network oscillations against variability in extrinsic parameters was studied by varying the maximal synaptic conductance parameters in a two-neuron network with reciprocal connections.

With restorative PIR, a small variability in the synaptic conductances affects dramatically the network behavior (Figure 5, A-D): identical maximal synaptic conductances generate oscillations but oscillations break down when the maximal synaptic conductances differ between the two cells. Oscillations with a purely restorative PIR are fragile to network variability.

By contrast, variability in the synaptic conductances is possible for a much larger range with regenerative PIR (Figure 5, E-H). The network frequency is also almost independent of the synaptic variability. Oscillations persist up to a variability higher than 80%. A source of slow-positive feedback in the PIR mechanism is therefore essential to robustness of network oscillations against network variability.

Exogenous noise

The robustness of the network oscillations against exogenous disturbances was investigated by adding a Gaussian white noise in the voltage equation to model the typical spike train input received from the many other unmodeled neurons [25]. We simulated a sixteen-neuron network with two populations, with a different noise source for each neuron (Figure 6).

The results are consistent with the robustness against variables. With a restorative PIR, oscillations are sensitive to noise and completely disappear with a noise level of 0.15. With a regenerative PIR, oscillations are robust to noise up to a level of 0.225.

We also evaluated how the noise affects the synchrony of the intra-population neurons by measuring the spectral density power of the local field potential (LFP) developed in each population. Figure 6 shows that synchrony decreases with the level of noise and that the LFP power is lower, for the entire noise intensity range, in the network with restorative PIR than with regenerative PIR.
Figure 4. Regenerative PIR makes network oscillations insensitive to intrinsic variability. Network connections: all the neurons in the first population are connected to all the neurons in the second population, and vice versa. A-D: restorative PIR. E-H: regenerative PIR. A and E: Grey color indicates presence of oscillations in the network, white indicates no oscillation. B-D and F-H: Raster plots with 0%, 25%, and 150% variability, respectively.

Robust modulation of network properties requires regenerative PIR

Neuromodulators can tune and reconfigure the network dynamics, affecting both the frequency and phasing of neurons [26,27]. For instance, in the Tritonia swim CPG, intrinsic modulation can produce an enhanced level of excitability, triggering the start of a circuit which activity is maintained after this initial signaling, generating an escape swimming response to particular aversive stimulus [28]. Neuromodulation can also switch the circuit between rhythms: in the crustacean stomatogastric ganglion, neuromodulators switch the circuit behavior from the fast pyloric rhythm, to two slower rhythms, the gastric mill rhythm and the cardiac sac rhythm [29]. In addition, neuromodulators can determine the active neuronal elements in the circuit or combine elements from different circuits into one [5,29].

Experimentally, the network properties, i.e. network frequency and duty cycle, can be modulated via both intrinsic neuron parameters and synaptic parameters on multiple timescales [5,6,27,29,34]. In this section, we investigate how the network behavior responded to these modulations, both with purely restorative PIR and regenerative PIR.
Figure 5. Regenerative PIR makes network oscillations insensitive to extrinsic variability. Network oscillations are robust towards synaptic variability with regenerative PIRs but not with restorative PIRs. A-D: restorative PIR. E-H: regenerative PIR. A and E: Grey color indicates presence of oscillations in the network, white indicates no oscillation. B-D and F-H: Membrane potentials with 0%, 50%, and 80% variability, respectively.

Figure 6. Regenerative PIR makes the network oscillations robust against exogenous noise. A and B: restorative PIR. C and D: regenerative PIR. A and C: Grey color indicates presence of oscillations in the network, white indicates no oscillation. B and D: The LFP maximum power, reflecting the population synchrony, is displayed in black and fitted by a linear regression curve in grey. A: Oscillations disappear with a moderate noise level. C: Oscillations persist up to a much higher noise level. B and D: The population synchrony is higher with regenerative PIR than with restorative PIR.

Robust modulation by extrinsic and intrinsic parameters with regenerative PIR

The high robustness brought by cellular regenerativity allows for the modulation by both extrinsic and intrinsic parameters (Figure 7). The network frequency and duty cycle—or phase relation—can be modulated independently. Modulations presented in Figure 7 can be reproduced in presence of high variability in the network thanks to the robustness of regenerative PIR (see for instance Figure 8, D).

Extrinsic parameters, i.e. the synaptic parameters, given intrinsic (cellular) characteristics, modulate the network frequency over a large range (Figure 7 A). Synaptic coupling is very plastic [35,36] and synapses are a primary target of modulators [34]. Synaptic currents are generated by the cooperation
Figure 7. Extrinsic and intrinsic parameters modulate the network frequency and duty cycle. With regenerative PIR, the network frequency and duty cycle can be modulated independently. The crosses below the graph indicate when the oscillations are destroyed. Eight temporal traces are given to exemplify the network behavior. A: Variation of the maximal synaptic conductance (black - bottom) and synaptic time constant (grey - top) modulates the network frequency. B: Variation of intrinsic neuron parameter $g_{PIR}$ (top) and variability between the intrinsic neuron parameter $g_{PIR}$ (bottom) modulates the duty cycle and the duty cycle ratio, respectively.

of several ion channel subtypes which can have slightly different kinetics. Variation of the synaptic parameters results from a variation of the contribution of all the subtypes. Absolute variation of the different ion channels influences the maximal conductance whereas their relative variation can modulate the time constant of the synaptic current that aggregates all the different subtypes in a model. Therefore, both the synaptic magnitude, $g_{syn}$, and the synaptic kinetics, $\tau_{syn}$, can be sources of modulation when varied in an admissible range (decreasing the value of $g_{syn}$ or increasing the value of $\tau_{syn}$ beyond a certain value destroys the oscillations). Variation of the $g_{syn}$ (resp. $\tau_{syn}$) parameter generates a 53% (resp. 54%) decrease in the network frequency. Such a span of modulation is indeed observed in physiological rhythms: for instance, there is a 60% decrease in frequency from sleep spindles ($\approx 10$ Hz) to slow-wave sleep ($\approx 4$ Hz) and a 70% decrease from gamma-band oscillations ($\approx 70$ Hz) to beta-band oscillations ($\approx 20$ Hz). Combination of the variation of both magnitude and kinetics (Figure 8 D) allows to explore an even larger range of network frequency.

Intrinsic parameters, i.e. the cellular parameters, given extrinsic (synaptic) characteristics, modulate the duty cycle and duty cycle ratio (Figure 7 B). Many neuromodulators act on the neuron intrinsic properties by altering the balance of conductances, modifying their excitability properties [27]. The maximal conductance of the PIR current is a natural candidate for modulation by intrinsic parameters. Figure 4 F-H, shows that the network frequency is barely affected by this intrinsic modulation. However, these intrinsic parameters are a source of modulation of the duty cycle and duty cycle ratio (Figure 7 B). Covariation of the maximal PIR conductance in both neuronal population leads to an increase in duty cycle ratio of 150%. Independent variation of the same parameter modulates the duty cycle ratio up to a 164% decrease. Variation in phase relation have been observed for instance in cats, during normal locomotion, where the shortening, by a factor two or three, of one of the phase (the extensor phase) leads to faster walking [37].
**Figure 8. The fragility of modulation with restorative PIR.** Modulation of the network frequency by varying synaptic parameters is robust with regenerative PIR but fragile with restorative PIR. A and C: restorative PIR; B and D: regenerative PIR. A and B: Grey color indicates presence of oscillations in the network, white indicates the absence of oscillations. Variation of the synaptic maximal conductance and the synaptic time constant with modulation directions in C and D, respectively. C and D: Variation of the maximal synaptic conductance (see legend): with no variability (solid black line), with weak variability in the intrinsic and synaptic parameters (dashed line), with strong variability (dotted line - no modulation possible for restorative PIR), and with a different synaptic time constant (solid grey lines - no modulation possible for restorative PIR). The crosses below the graph indicate when the oscillations are destroyed. Four temporal traces are given to exemplify the network behavior.

**Fragile modulation with restorative PIR**

Our computational model suggests that modulation with restorative PIR is so fragile that it is unrealistic. Variation of intrinsic parameters destroys oscillations very rapidly (Figure 4, A-D). Regarding variation of extrinsic parameters, similar conclusions can be drawn: variations of $g_{syn}$ allow for a modulation of the network frequency but for a much shorter range than with regenerative PIR (Figure 5). Moreover, this modulation is very fragile. The modulation range shrinks drastically with weak variability and disappears completely with high variability (Figure 5, C, dashed and dotted lines). Variation of $\tau_{syn}$ is almost impossible (Figure 5, A and C): $\tau_{syn}$ must lie in a very specific time-scale for the oscillations to develop in the network. The modulation requires a tight coupling between intrinsic and extrinsic parameters: the network oscillations are a direct reflection of the unicellular behavior. The oscillation frequency is set by the neuron intrinsic dynamics and no variation can be induced by the synaptic dynamics.
Discussion

Cellular slow regenerativity is essential to network robustness and modulation

The main message of this paper is to highlight the role of slow regenerativity, a cellular excitability property, in endowing network oscillations with robustness and modulation properties that seem ubiquitous in physiological neural networks. An ionic current is slowly regenerative if it provides a source of positive feedback around resting potential in the slow time-scale of repolarization [18]. The importance of this cellular property was assessed in one of the simplest and best understood network oscillations mechanisms, the anti-phase rhythm observed between two homogenous populations of neurons reciprocally connected by inhibitory synaptic (GABA) connections. Many earlier studies have emphasized the role of post-inhibitory rebound (PIR) at the cellular level as a core mechanism for the network oscillation, and have identified $I_h$ and $I_{CaT}$ as two distinct ionic currents that can participate in the PIR. Our novel contribution is to observe that the cellular PIR will enable a robust and modulable network oscillation only if it is regenerative, that is, in the presence of a slow-regenerative ionic current. Because $I_h$ is ultra-slowly restorative and $I_{CaT}$ is slowly regenerative, our paper suggests a novel and somewhat fundamental complementarity between T-type calcium and $I_h$ channels in PIR mechanisms.

As a source of positive feedback, regenerative currents make the PIR endogenous, that is, robust to intrinsic and extrinsic sources of variability. As a consequence, a regenerative PIR allows for network oscillations that are robust and modulable. The network oscillation is robust because it can sustain large variability across the neuronal population both in intrinsic (cellular) and extrinsic (synaptic) parameters. It is also modulable because the frequency and phase properties of the oscillation can be controlled over a broad range by a relative modulation of extrinsic or intrinsic conductances. Our computational model illustrated that this robustness and modulation properties are lost when the PIR is purely restorative.

Positive feedback as a source of endogenous behavior

Slow regenerativity is nothing but a source of positive feedback in the slow time-scale ($\approx 10ms$) of repolarization. It is a slow analog of the positive feedback brought by sodium activation in the fast time-scale ($\approx 1ms$) of spike upstroke. In previous work [18], we showed that this positive feedback is essential to bistability at the cellular level, allowing for the robust coexistence of rest and oscillations at the cellular level. We subsequently showed in [17] that this positive feedback is essential for modulation and robustness of bursting behaviors. Here we show that the same positive feedback at the cellular level is also essential for robustness and modulation at the network level. The common feature of the positive feedback in those three phenomena is that it makes the neuronal excitability in the slow time-scale an endogenous property, robust to intrinsic and extrinsic variability. Making a behavior endogenous is the very nature of positive feedback and has been emphasized in a number of contexts. The results in this paper are in line with the discussion of the role of positive feedback in other biological models, such as for instance the biochemical mechanisms underlying the mitotic oscillator [38][40]: the oscillator is endogenous and robust in the presence of positive feedback, whereas it becomes exogenous and entrainable when the source of positive feedback disappears. The importance at the network level of positive feedback at the cellular level is thought to be general and not specific to the case study of half-center oscillators chosen in this paper for its simplicity and physiological relevance.

Network regulation by tuning a cellular balance

There is ample evidence that the balance between slow-regenerative and slow-restorative currents is tightly regulated in many neurons [18]. In the context of half-center oscillators studied in the present paper, this balance is naturally regulated by the balance between $I_h$ and $I_{CaT}$, the two main currents that contribute to PIR. This balance is a direct target of neuromodulators, see e.g. [41], and provides a
powerful control mechanism to adjust the endogenous or exogenous nature of network oscillations at the cellular level, that is, in spatial and temporal scales that cannot be controlled by synaptic plasticity.

**Restorative and regenerative PIR in half-center oscillations models**

There is a rich literature on computational models of oscillations generated by reciprocal inhibition. Half-center oscillators have been used to model rhythmic motor outputs in many invertebrates and vertebrates \[3,8,11\]. In a different context, models of thalamocortical spindle oscillations suggest that the rhythm originates from the thalamic reticular nucleus, which consists in interacting inhibitory nonoscillatory neurons \[14,42–44\].

It is of interest to observe the varying degree of cellular regenerativity in published models of half-center oscillators. Early models are conductance-based and usually include at the cellular level both \(I_h\) and \(I_{CaT}\), the two main physiological currents controlling the regenerative nature of PIR \[11,43,45–47\]. However, network computational studies often lead to a subsequent mathematical simplifications of the cellular details and the cellular balance between slow negative and positive feedback is often lost in this reduction process. A frequent simplification in the literature (see e.g. \[14,15,42,48,49\]) is to resort to a steady-state approximation of the calcium activation in the same way as it is normally done for sodium activation. But this approximation rests on neglecting fast dynamics, which amounts to consider calcium channels as a source of fast rather than slow positive feedback (see Figure 2). The resulting reduced models have therefore lost their source of slow regenerativity, which makes them unsuitable for robustness and modulation studies at the network level.

The alternative model reduction consists to model the cellular level as Morris-Lecar type of neurons, retaining the slow calcium currents but neglecting the fast sodium currents \[12,13\]. Those models do retain the slow positive feedback source necessary for robustness but they lose the modulation capabilities illustrated in the present paper because the network interconnection properties are spike-dependent. This prevents exogenous modulation of the rhythm. In addition, if sodium spikes were added to a Morris-Lecar neuron with the addition of the spike currents (as suggested in \[50\]) while keeping the calcium activation at steady-state the slow regenerativity would be destroyed.

It should be noted that it is perfectly possible to derive reduced neuronal models that do retain the balance of slow positive and negative feedback as an explicit parameter, see e.g. the recent models in \[17,51\]. The results of the present paper suggest that it is an important feature to retain in a simplified model aimed at network computational studies.

**Methods**

All the numerical simulations and analyses were performed with MATLAB, MathWorks. The models were implemented in a MATLAB code and simulated using a forward Euler method with a time step of 0.005ms.

**Conductance-based model**

The conductance-based model is inspired from a cellular model much studied in the CPG literature, the neurons of the crab stomatogastric ganglion (STG) \[21,52\]. The model contains the standard Hodgkin-Huxley (HH) currents \[53\]: the sodium current, \(I_{Na}\), a fast depolarizing current, and the potassium current, \(I_{Kd}\), a slower hyperpolarizing current, plus a leak current, \(I_l\). \(I_{Na}\) and \(I_{Kd}\) are responsible for the generation of action potentials. All parameters are similar to the ones given in \[21\], except for a slight modification in the sodium steady-state activation variable (25.5 becomes 35.5). The maximal conductances are \((60,15,0.035)\) for \((g_{Na},g_{Kd},g_l)\).
The model also contains a single PIR current which aggregates the effect of $I_h$ and $I_{CaT}$. This current is a slightly modified version of the $I_{CaT}$ current of [21]: the calcium reversal potential is fixed here to 120mV and we insert small modifications in steady-state activation and inactivation variables (27.1 becomes 57.1 and 32.1 becomes 82.1). The maximal conductance is $g_{PIR} = 0.3$. Independently from the maximal conductance, the activation time constant controls the balance between restorative and regenerative PIR: an instantaneous activation—i.e. steady-state approximation of the activation—makes the PIR restorative, modeling a PIR dominated by $I_h$ current, whereas an activation in the slow time-scale gives a regenerative PIR, modeling a PIR in the presence of a slow calcium current. From a modeling viewpoint, modulating the speed of the activation time constant is thus a convenient way to modulate the regenerativity of PIR without affecting its maximal conductance.

Network model

To compare a network with purely restorative PIR with a network with regenerative PIR, the simulations were done with an instantaneous activation time constant for restorative PIR and slow activation for regenerative PIR.

The gamma-aminobutyric acid (GABA) synaptic connections are made with exponential synapses of the GABA$_A$ type. The synaptic current between two neurons takes the form [44]:

$$I_{syn} = g_{syn} (V - V_{syn}) \frac{1}{N} \sum_{j=1}^{N} s_{A_j},$$

$$\frac{ds_{A_j}}{dt} = k_f A x_{\infty}(V_j) \left(1 - s_{A_j}\right) - k_r A s_{A_j},$$

$$x_{\infty}(V) = \left[1 + \exp \left(-\frac{V - \Theta_s}{\sigma_s}\right)\right]^{-1},$$

where $V_j$ is the presynaptic membrane potential and $N$ the number of presynaptic neurons. $\Theta_s = -45mV$, $\sigma_s = 2mV$, $g_{syn} = 4mS/cm^2$, $V_{syn} = -75mV$, $k_f A = 2ms^{-1}$, and $k_r A = 0.1ms^{-1}$.

Analyses

For the detection of presence of oscillations in the network, we determine if there exist two consecutive spikes, within a maximum of 200ms, in all the simulated neurons, during the last 3s of the simulation. If the answer is yes, this means that oscillations are maintained in all the neurons for the entire simulation period. In the opposite case, oscillations are not maintained.

The LFP dynamics result from the collective synaptic activity of the neuronal population [54]. The LFP dynamics, for each population, is modeled by the normalized sum of the $I_{syn}$: $LFP = \sum_{i=1}^{N} I_{syn_i}/N$, where $N$ is the number of neuron in the population. The LFPs are low-pass filtered with cutoff frequency of 100Hz via a one-dimensional digital filter to reflect the use of macro-electrodes in LFP acquisition. Only the stationary phase is considered (after the first 2.5s of initialization). The power spectral density is computed for each LFP with the PSD function in MATLAB. The maximum, except the DC value, of the power spectral density is extracted and the maximums for the two populations are averaged to reflect the LFP power.

Network oscillations of Figure [1]

A cell model with restorative PIR is used in this network simulation. The applied current, $I_{app}$, on both neurons takes a value of $-0.55nA$. During the hyperpolarization, the applied current on neuron 1 drops to $-1.1nA$. 
Literature models of Figure 2

The cell models are directly taken from the literature. For row 1, we use the model described in [55] with the $I_h$ kinetics taken from [21] with a small modification of the steady-state activation variable (70 becomes 80) and $g_h = 0.04$. The applied current, $I_{app}$, takes a constant value of $-0.55nA$ and a value of $-1.95nA$ for 500ms. For $I_{CaT_{inst}}$, the cell model is directly taken from [56] and the $I_{app}$ current takes a constant value of $-10nA$ and a value of $-50nA$ for 2s. For row 2 and 3, the cell model is directly taken from [57] and [58], respectively. In both cases, the $I_{app}$ current takes a constant value of 0nA and a value of $-0.3nA$ for 250ms. For the time-scales and time constants representation, each time constant is set in the time-scale to which it contributes the most.

Cell simulations of Figure 3

The $I_{app}$ current takes a constant value of $-0.55nA$ and a value of $-1.95nA$ for 500ms. For the first row, the extrinsic parameter, the $I_{app}$ current, varies by 0.1nA for its value after the hyperpolarization. For the second row, the intrinsic parameter, the maximal conductance for the PIR current, $g_{PIR}$, varies from 0.2 to 0.4.

Network simulations of Figure 4

The two populations, each composed of eight neurons, are connected all-to-all with the synaptic current described in the previous section. Variability in the intrinsic neuron parameter $g_{PIR}$ is introduced by picking out of a variability range (random distribution) around the mean value $g_{PIR} = 0.3$. The variability level quantifies the variation range around this mean parameter value.

Network simulations of Figure 5

Variability in the maximal synaptic conductances $g_{syn}$ is introduced by picking the extremities of a variability range around a mean value $g_{syn} = 4$. The variability level quantifies the variation range around this mean parameter value.

Network simulations of Figure 6

The two populations, each composed of eight neurons, are connected all-to-all with the synaptic current described in the previous section. A Gaussian white noise is added in the voltage equation to model the typical spike train input received from the many other unmodeled neurons [25]. The noise is modeled by $\sqrt{2D}\xi(t)$, where $D$ is the noise intensity and varies in the simulation, and $\xi(t)$ is drawn from a normal distribution with zero mean and unitary standard deviation.

Network simulations of Figure 7

The maximal synaptic conductance, $g_{syn}$, the synaptic time constant, $1/k_{rA}$, and the maximal PIR conductance, $g_{PIR}$, vary simultaneously for the two neurons. The variability is introduced by varying the $g_{PIR}$ independently for each neuron with a mean value of 0.3, with a mismatch as indicated on the x axis. The temporal traces are obtained for fixed parameter values. The parameter set is as indicated by the arrows.

Network simulations of Figure 8

The maximal synaptic conductance, $g_{syn}$, and the synaptic time constant, $1/k_{rA}$, vary simultaneously for the two neurons. The graphs for the evolution of $f_{network}$ are done with $k_{rA} = 0.1$ and $k_{rA} = 0.25$ for the
black and grey lines, respectively. Weak variability in the network is introduced with a mismatch of 1.5 in the maximal synaptic conductance values around 0.4 and a mismatch of 0.06 in the intrinsic neuron parameter $g_{PIR}$ around 0.3. Strong variability in the network is introduced by doubling the mismatch values. The temporal traces are obtained for fixed parameter values and no variability. The parameter set is as indicated by the arrows.

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