Control by neuromodulation: a tutorial.

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***Abstract*— This tutorial provides an introduction to the topic of neuromodulation as an important control paradigm for natural and artificial neuronal networks. We review how neuromodulation modulates excitability, and how neuromodulation interacts with homeostasis. We stress how modulating nodal excitability provides a robust and versatile control principle to dynamically reconfigure the connectivity of rhythmic circuits and to shape the spatio-temporal synchrony of large populations.**

***Index Terms*— Neural circuits, neuromodulation, excitability, homeostasis, robustness, adaptation.**

I. Introduction

Neuromodulation is an important control principle of neuroscience. In a physiological context, neuromodulation designates the regulation of the electrical activity of neuronal circuits by ignaling molecules called neuromodulators. They include ACh, dopamine, norepinephrine, GABA, glycine, glutamate, serotonin, histamine, octopamine, and neuropeptides. In a medical context, neuromodulation designates the increasing body of technologies aiming at interacting with the electrical activity of neuronal circuits. Minimally invasive technologies have been rapidly developing in the recent years. They include electromagnetic stimulation (e.g. deep-brain stimulation as a treatment for Parkinson's disease), pharmacological drug delivery, and optogenetics. The mechanisms of medical neuromodulation are still poorly understood and largely empirical, but, ultimately, they can be regarded as an external interaction with the internal physiological mechanisms of neuromodulation.

Neuromodulation is a natural entry point to neuroscience for control theorists and control engineers. A theory of physiological neuromodulation is ultimately a control theory of neuronal circuits. One of the earliest books on neuromodulation is entitled *Neuromodulation: The Biochemical Control of Neuronal Excitability* [35]. It could serve as a title of this tutorial. The recent review [48] by Eve Marder should speak to control theorists as a remarkable invitation to study neuronal circuits. The following two quotes of the paper are illustrative: "Because the output of all biological circuits results from the interaction of many nonlinear elements, computational models are needed to understand them. How realistic do these models need to be, and what data are needed to constrain these models? How will modulation alter these processes? " and "How can highly modulated circuits be stable in the face of parameter changes brought about by modulation?" The central questions of neuromodulation are all control theoretic in nature: How do neuronal circuits cope with uncertainty, heterogeneity, and variability ? How do neuronal circuits dynamically reconfigure to process sensory signals and execute motor tasks ? Medical neuromodulation is largely regarded as the future of neuroengineering and investigated as a potential treatment for a rapidly expanding range of pathologies.

Traditionally, the emphasis in modeling the nervous system has been on *neurotransmission* rather than *neuromodulation*. The focus of neurotransmission is on the excitatory or inhibitory synaptic transmission of electrical signals in neuronal networks. In contrast, neuromodulation is about the permanent modulation (another name for control) of cellular or synaptic properties of neurons by neuromodulators. Neuromodulators are released by specific sets of neurons. Those neuromodulatory neurons are localized in specific regions of the brains but they project broadly. Neuromodulation can radically alter the processing properties of neurons and synapses over short time scales and large spatial scales. Neuromodulators are major players in the control of neuronal circuits and suggest a diversity of possible behaviors for a given connectome.

The focus of this tutorial is to introduce some of the basic mechanisms of neuromodulation in a control theoretic language. We minimize the reference to biological details and provide cartoon illustrations of general principles that could also be of potential importance in artificial neuromorphic circuits or artificial neural networks.

The aim of this tutorial is to inspire control theorists and control engineers. Specific examples will be selected to illustrate that neuromodulation raises novel control questions that directly connect the classical language of circuit theory to some of the most fascinating challenges of neuroscience and neuroengineering.

II. A brief history of neuromodulation

Irrespective of background, many engineers will have an informal picture of a neuron as an excitable electrical device, coupled in a circuit to sensory organs, muscles and other neurons. This view emerged early in the history of physiology, where the pioneering work of Galvani (1737-1798) and Ramon y Cajal (1852-1934) respectively revealed the

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electrical basis of neural activity and unpicked the intricate 'wiring' of the brain as a network of interconnected cells. Later work in the early 20th century revealed that neurons signal in discrete pulses, or action potentials [1], [43]. It was not obvious at the time that the interconnections - synapses - between circuit elements were chemical in nature: neurons influence their neighbours by secreting tiny puffs of amino acids, peptides and other small molecules [6], [7], [16], [70].

Neurotransmitters act as a chemical key, binding to receptor proteins that are structurally maintained in close apposition to their site of release. Receptor proteins, in turn, are physical pores that selectively allow ions to pass when open. The action of synaptic transmission can be conveniently and accurately modelled as a variable conductance in series with a potential difference that represents the electrochemical driving force of different ionic species. This driving force can be negative or positive with respect to the resting membrane voltage of a neuron. Synaptic transmission may thus excite or inhibit a target. Similarly, the maximal conductance of a synapse may vary.

Since the 1930s it was known that there are multiple types of neurotransmitters [6] and distinct types of neurons that secrete specific neurotransmitters. Accordingly, there are multiple types of neurotransmitter receptors, each with its own biophysical characteristics. To a loose approximation, one can summarize this picture of neural circuits as a collection of excitable elements that are interconnected via positive or negative (excitatory or inhibitory) synapses.

This picture of a neural circuit as a network of excitable elements with signed interconnections is very appealing. It suggests that circuit principles in electrical engineering can be directly applied to understand the function of any neural circuit, provided the connectivity (or wiring diagram) and the signs and relative strengths of synapses are known [66], [69].

The 70s saw a surge in interest in mapping the connections of small and experimentally tractable circuits [22], [3], [36]. Often, these circuits belonged to molluscs, crustaceans and other simple marine organisms that were found to have large, easily identifiable and physically robust nervous systems that controlled relatively simple behaviors [46]. The belief at the time was that the schematic, or wiring diagram of a neural circuit would be sufficient to explain its function, modulo some standard system identification applied to the circuit elements themselves.

Over the course of the 70s and 80s this belief unravelled [63]. Most notably, the doctrine that synapses represent the sole inputs to neurons was found to be wrong. Similarly, the convenient taxonomy of neurons into two classes, 'excitatory' and 'inhibitory,' turned out to be incorrect, as did the assumption that neurons can only secrete one type of neurotransmitter.

Pioneering work in invertebrate motor circuits revealed the existence of chemical signals that act diffusively in the circuit [30], [18], [9], [40], [27], [31], [32]. These signals, termed *neuromodulators*, are secreted by neurons in a similar way to classical neurotransmitters. However, instead of acting only at the synapse, many neuromodulators diffuse long distances and are capable of targeting populations of neurons. Moreover, the mode of action of many neuromodulators is fundamentally different to classical neurotransmitters. Instead of merely exciting or inhibiting neurons, neuromodulators – as their name suggests – *modulate* the biophysical properties of target neurons.

In later sections we will clarify the kinds of biophysical properties that are affected by neuromodulators. Informally, these can include synaptic conductances or the *intrinsic* conductances that control the excitable behaviour of a neuron. Neuromodulators can thus directly reconfigure the wiring diagram of a circuit by changing interconnection strengths. They can 'switch' the nodes in the circuit from generating discrete pulses to oscillations. They can also alter the degree of excitability of neurons, making otherwise quiescent circuits highly active.

Contemporary neuroscience research has been transformed by experimental methods that allow neural circuits in more complex organisms, including humans, to be mapped in increasing detail. Modern connectomics allows exhaustive mapping of the connectivity of entire nervous systems. Similarly, recording and stimulation technology allows measurement and control of neurons at a level of precision that permits intentions, sensations and actions to be reliably decoded in awake, behaving animals.

This wave of technological progress understandably fuels promises that neural circuits in 'higher' organisms can be understood mechanistically. This excitement mirrors the hopes that were ignited over 40 years ago in small invertebrate circuits. Paradoxically, the same lessons about neuromodulation are being rediscovered [38], [44]. The confounds, surprises and shifts in thinking that followed the discovery of neuromodulation are playing out for a second time on a much bigger scale. Progress in neural engineering as well as basic science requires us to develop a systems theoretic approach to neuromodulation. Medical devices such as brain implants minimally exploit this fundamental model of signalling to dramatic effect, essentially reversing the debilitating effects of Parkinson's disease at the flick of a switch [2]. There has never been a greater need for a solid theoretical foundation for understanding neuromodulation.

III. Neuromodulation as a control problem

A. Models and system properties

A neuronal circuit is modelled as an electrical network of N nodes (neurons) with nodal voltages V_i and passive dynamics

$$C_i\dot{V}_i = -g_i(V_i - E_i) + I_i,\ 1 \leq i \leq N. \tag{1}$$

The current I_i into node i is the sum of (possibly many) currents determined by three types of conductances: intrinsic (g_{ion}), synaptic (g_{syn}), and diffusive (g_{gap}). Each resulting current into node i obeys Ohm's law: $I_{ion} = g_{ion}(V_i - E_{ion})$, $I_{syn} = -g_{syn}(V_i - E_{syn})$, and $I_{gap} = -g_{gap}(V_i - V_j)$. Without those currents, the neuron model reduces to a

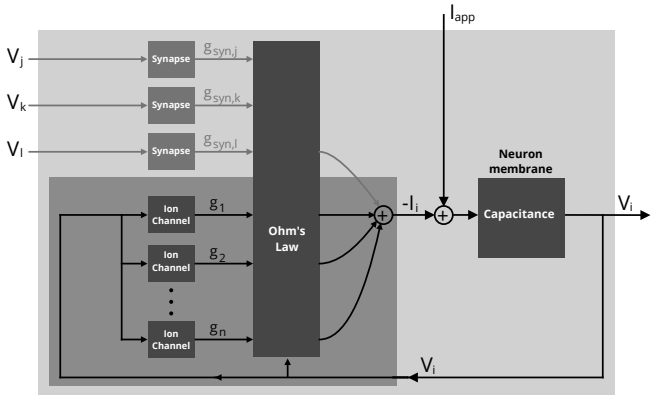

Fig. 1. The block diagram of a neuronal model. Intrinsic conductances are *feedback* amplifiers. Synaptic conductances are *feedforward* amplifiers.

RC circuit with capacitance C_i and resistance $R_i = \frac{1}{g_i}$. The (battery) potentials E_i, E_{ion}, and E_{syn} are constant parameters. Also the gap conductances g_{gap} are constant parameters. An additional current I_{app} is often added in the model as well to mean an external current *applied* to the neuronal circuit.

Electrical conductances account for gap junctions (or electrical synapses), modeled as a resistor of conductance g_{gap} between two nodes i and j. They model diffusive couplings in the electrical network. What makes neuronal circuits distinct from other electrical networks is that intrinsic conductances and synaptic conductances are *voltage* dependent. Intrinsic conductances depend on the nodal voltage V_i whereas synaptic conductances depend on the pre-synaptic voltage.

Intrinsic and synaptic conductances are modeled as nonlinear *voltage amplifiers*. They are difficult to model because they account for the mean-field gain at a cellular scale of discrete events at a molecular scale. Their gain is amplitude dependent and has fading memory. A simple conductance model that captures those two properties has the form

$$\begin{array}{rcl} g & = & \bar{g}\, S(V_f) \\ \tau_f \dot{V}_f & = & -V_f + V \end{array} \tag{2}$$

The parameter $\bar{g}$ is called the maximal conductance. The nonlinearity $S(\cdot)$ modulates the conductance in a normalized range $[0, 1]$. It has sigmoidal shape, meaning that the differential gain $S'(\cdot)$ is bell-shaped and vanishes away from an amplitude of maximal activation. The time-constant τ models the fading memory of the amplifier.

The key difference between intrinsic and synaptic conductances is illustrated in Figure 1. Intrinsic conductances are feedback amplifiers of the nodal voltage whereas synaptic conductances are feedforward amplifiers from the presynaptic voltage to the nodal voltage. Feedforward neuronal networks necessarily exclude intrinsic conductances.

In the absence of intrinsic and synaptic conductances, a neuronal network is a passive electrical network, made of passive nodes interconnected by passive resistors. The intrinsic conductances equip the nodal dynamics with feedback amplifiers. The synaptic conductances augment the passive interconnections with feedforward amplifiers. The mathematical modeling of a neuronal network as passive electrical nodes interconnected by nonlinear voltage amplifiers is rather general. It encompasses many mathematical models of both animal and artificial neural networks. We review three examples of different nature below.

Example 1: [Hopfield model] The seminal Hopfield model [33] of associate memories consists of N nodes with nodal dynamics

$$C\dot{V}_i = -\frac{V_i}{R_i} + \sum_{j=1}^{N} w_{ij} S(V_j) + I_{app,i} \tag{3}$$

Each current $w_{ij}S(V_j)$ models a synaptic current from node j to node i. The term $S(V_j)$ is a sigmoidal amplifier of the presynaptic voltage V_j. The synaptic weight w_{ij} is a parameter that is positive for an excitatory synapse and negative for an inhibitory synapse. The simplification $I_{syn} = -g_{syn}(V_j)(V_i - E_{syn}) \approx w_{ij}S(V_j)$ is a simplification of the Ohmic dependence when the battery potential E_{syn} is always larger than V_i (excitatory) or always smaller than V_i (inhibitory). Also the dynamics of the amplifier is neglected in Hopfield model ($\tau_f = 0$), which corresponds to a synapse with instantaneous activation. ⌟

Example 2: [Hodgkin-Huxley model] The seminal model of Hodgkin-Huxley [29] consists of a single neuron with dynamics

$$C\dot{V} = -g_l(V - V_l) - g_{\mathrm{Na}}(V - E_{\mathrm{Na}}) - g_{\mathrm{K}}(V - E_{\mathrm{K}}) + I_{app} \tag{4}$$

The model includes two intrinsic conductances: a potassium conductance g_{K} and a sodium conductance g_{Na}. The model of the potassium conductance is

$$\begin{array}{rcl} g_{\mathrm{K}} & = & \bar{g}_{\mathrm{K}} n^4 \\ \tau_n(V)\dot{n} & = & -n + n_\infty(V) \end{array} \tag{5}$$

while the model of the sodium conductance is

$$\begin{array}{rcl} g_{\mathrm{Na}} & = & \bar{g}_{\mathrm{Na}} m^3\, h \\ \tau_m(V)\dot{m} & = & -m + m_\infty(V) \\ \tau_h(V)\dot{h} & = & -h + h_\infty(V) \end{array} \tag{6}$$

Both the potassium and the sodium conductances have the interpretation of a fading memory amplifier of the voltage V. In neurophysiology, the variables n, m, and h are called gating variables. They are all defined in the finite range $[0, 1]$. The variables n and m are called *activation* variables because $n_\infty(\cdot)$ and $m_\infty(\cdot)$ are monotonically increasing (with sigmoidal shape). The variable h is called an inactivation variable because $1 - h_\infty(\cdot)$ is sigmoidal. All the parameters of Hodgkin-Huxley model were determined through careful curve fitting of experimental data. Modeling a particular intrinsic conductance with one activation and one inactivation variable in the same way as in Hodgkin-Huxley model is still the most prevalent conductance model in today's detailed models of neurophysiology. Those models are called conductance-based models. ⌟

Example 3: [Neuromorphic circuit] The artificial circuit recently proposed in [59] consists of a single neuron with dynamics

$$\begin{array}{rcl} C\dot{V} & = & -I_p(V) - \sum I_x^{\pm} + I_{app} \\ I_x^{\pm} & = & F_x^{\pm}(V_x) \\ \tau_x \dot{V}_x & = & -V_x + V \end{array} \quad (7)$$

Here the passive current $I_p(V)$ is a nonlinear resistor. Each active current $I_x^{\pm}$ models an independent current source controlled by a voltage amplifier. Each amplifier has a sigmoidal static characteristic F_x with positive or negative derivative F_x'. The dynamics of each amplifier is a first-order lag. Such active circuit elements have an elementary realization with MOSFET-based transconductance amplifier operating in the weak inversion regime. They are core circuit elements of neuromorphic analog architectures proposed in [52]. The circuit architecture is neuromorphic in that each current source mimicks in silico the contribution of a specific intrinsic conductance in a physiological neuron.

An early example of neuromorphic circuit is the circuit of Nagumo [53] designed to reproduce in silico the mathematical model proposed by FitzHugh [17] to approximate the behavior of Hodgin-Huxley model. FitzHugh-Nagumo circuit corresponds to model (7) with the passive current $I_p(V) = \frac{V^3}{3}$, an instantaneous negative conductance current $I^-(V) = -V$, and a slow positive conductance current $I_s^+(V_s) = kV_s$, with a slow-lag $\tau_s > 0$. In Nagumo's circuit realization, the slow current flows through an inductor in series with a resistor, whereas the fast current models the negative conductance of a tunnel diode. ⌟

B. Control by neuromodulation

Neuromodulators modulate intrinsic and synaptic conductances. We model this external control by considering the maximal conductance parameters $\bar{g}$ as control variables. This mean-field parameter accounts for a variety of neuromodulation mechanisms at the molecular level. Those mechanisms are not discussed in the present tutorial. Regardless of the underlying molecular mechanisms, the neuromodulation of a neuronal network can be studied by analyzing the sensitivity of the network behavior to specific maximal conductance parameters.

Neuromodulators modulate intrinsic conductances as much as they modulate synaptic conductances. Historically, the modulation of synaptic conductances has received much more attention than the modulation of intrinsic conductances. This is because the maximal conductances of synaptic conductances, or synaptic weights, are also the control parameters of synaptic plasticity. They are adapted via various rules in order to model learning capabilities of the network. Learning by adaptation of synaptic weights has been extensively studied both in animal and artificial models. Often those models exclude intrinsic conductances and have a purely feedforward structure.

Neuromodulation differs from synaptic plasticity. It affects intrinsic conductances as much as synaptic conductances. To stress that difference, the illustrations in this tutorial will only consider the neuromodulation of intrinsic conductances.

By definition, the modulation of an intrinsic conductance is the modulation of a feedback amplifier. This is why the question of neuromodulation is fundamentally about the sensitivity analysis of a feedback system, a core question of control theory. In a single cell, a neuromodulator modulates the *loop gain* of a feedback system. The many-to-one structure of the feedback block diagram in Figure 1 suggests the richness of neuromodulation as a control mechanism: a single neuromodulator can modulate the gain of many intrinsic conductances, and many distinct neuromodulators can modulate the gain of a single conductance. In short, neuromodulation is an exquisite source of loop shaping. In a network, neuromodulation can affect the intrinsic conductances of many neurons. It raises the interesting question of controlling a network by shaping the sensitivity of the nodes rather than by shaping the sensitivity of the interconnections. In a neuromorphic circuit realization like the one discussed in Example 3, the maximal conductance of each element is controlled by the base current of a transistor.

Returning to the basic model architecture (1) and the block diagram in Figure 1, one can think of each neuron of a neuronal circuit as a simple passive device controlled by a parallel array of feedback amplifiers (the *intrinsic* conductances) and a parallel array of feedforward amplifiers (the *extrinsic* conductances). Neuromodulation makes the gain of each of those amplifiers a potential control variable. In the language of circuit theory, each neuron is a one-port circuit controlled by many parallel voltage amplifiers. Each voltage amplifier is potentially under the control of one or several neuromodulators.

C. Excitability, thresholds, and loop-shaping

To appreciate the importance of neuromodulation as a loop-shaping mechanism, it is instructive to connect loop-shaping to excitability. Neuronal excitability is a key property of neuronal networks. Excitable systems are characterized by a sharply distinct sub-threshold and supra-threshold behaviors [64]. The sub-threshold behavior of an excitable system is its small-signal behavior : it is determined by the passive response of the neuron for small voltage deviations from equilibrium. The supra-threshold behavior is its large-signal behavior. It is determined by the all-or-none response of the neuron for voltage variations exceeding a threshold. This all-or-none response takes the form of specific discrete events such as spikes. Figure 2 illustrates the sub-threshold and supra-threshold behaviors of Hodgkin-Huxley model.

The existence of a threshold is easy to understand in the static approximation of a neuronal model :

$$(C\dot{V} =)0 = -I(V) + I_{app} \quad (8)$$

The curve $I(V)$ is called the I-V curve of the neuron. The existence of a threshold is related to the monotonicity of the I-V curve. If the curve $I(V)$ is monotone, there is no (static) threshold : the variation of voltage is a monotone function of the variation of current. Instead, a non-monotonic

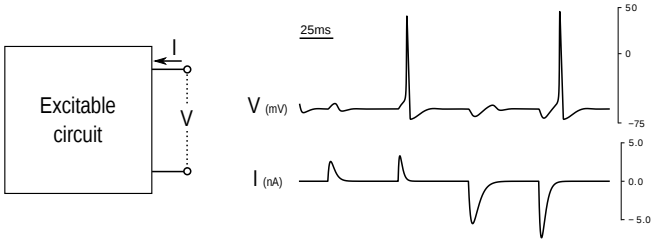

Fig. 2. The threshold property of an excitable circuit illustrated with Hodgkin-Huxley model. The large voltage excursion ($\approx 100mV$) over a short time-interval ($\approx 5ms$) is called an action potential or a spike.

I-V curve has a threshold at the minimum voltage of zero conductance, that is the point V where $I'(V) = 0$. A continuous variation of the current around the threshold produces a discontinuous variation of the voltage. Around the threshold, the static model is ultra-sensitive: a small variation of the current results in a large variation of the voltage. Hence the neuron static model has a threshold if and only if the I-V curve has a range of *negative differential conductance*, that is a voltage range where $\frac{dI}{dV} < 0$. A range of negative conductance implies that the model is non invertible and has ultra-sensitivity around the point of zero conductance $\frac{dI}{dV} = 0$. In a static model, the point of zero conductance identifies the threshold.

In the block-diagram representation of Figure 1, the differential conductance of the neuron is equal to the differential loop gain of the feedback system. As an example, consider the static approximation of Hodgkin-Huxley model

$$I_{app} = g_l(V - V_l) + g_{\rm Na}(V)(V - E_{\rm Na}) + g_{\rm K}(V)(V - E_{\rm K})$$

with

$$\begin{array}{rcl} g_{\rm Na}(V) & = & \bar{g}_{\rm Na} m_\infty^3(V)\, h_\infty(V) \\ g_{\rm K}(V) & = & \bar{g}_{\rm K} n_\infty^4(V) \end{array} \qquad (9)$$

The linearized equation around V is

$$g_{\rm tot}\delta V = \delta I_{app} - (g'_{\rm Na}(V)(V - E_{\rm Na}) - g'_{\rm K}(V)(V - E_{\rm K}))\delta V$$

where the total conductance is defined as

$$g_{\rm tot} = g_l + g_{\rm Na}(V) + g_{\rm K}(V).$$

In the terminology of control theory, this circuit admits the representation of a unity feedback system with loop gain $L(V)$. The loop gain is the function

$$L(V) = \frac{g'_{\rm Na}(V)(V - E_{\rm Na}) + g'_{\rm K}(V)(V - E_{\rm K})}{g_{\rm tot}}.$$

The sensitivity function $S = \frac{1}{1+L}$ is

$$S(V) = \frac{g_{\rm tot}}{g_{\rm tot} + g'_{\rm Na}(V)(V - E_{\rm Na}) + g'_{\rm K}(V)(V - E_{\rm K})}$$

The sensitivity of the feedback system becomes infinite for the threshold voltage at which the total differential conductance $g_{\rm tot} + g'_{\rm Na}(V)(V - E_{\rm Na}) + g'_{\rm K}(V)(V - E_{\rm K})$ vanishes.

The reader will observe that for any voltage $V \in [E_{\rm K}, E_{\rm Na}]$, the terms $g_{\rm tot}$ and $g'_{\rm K}(V)(V - E_{\rm K})$ are always positive. Only the term $g'_{\rm Na}(V)(V - E_{\rm Na})$ is negative when $g'_{\rm Na}(V) > 0$. In other words, the potassium conductance always provides negative feedback amplification and only the sodium conductance can provide positive feedback amplification. Ultra-sensitivity arises as a balance between positive and negative feedback amplification. By modulating the gains $\bar{g}_{\rm Na}$ and $\bar{g}_{\rm K}$, neuromodulation can regulate this balance. This indicates the core reason why the neuromodulation of intrinsic conductances provides feedback control of excitability. In contrast, as feedforward amplifiers, synaptic conductances do not contribute to the loop-shaping of the sensitivity function.

D. Dynamic conductances

Excitability and its threshold property are harder to quantify in a nonlinear dynamical model of the neuron. One way to proceed is to consider the linearized model of the neuron around an equilibrium voltage. The loop-gain and the sensitivity functions in the previous section then become transfer functions of the linearized models parametrized by the equilibrium voltage : $L(s;V)$ and $S(s;V)$. The static quantities defined in the previous section correspond to the static gains $L(0;V)$ and $S(0;V)$. This approach however ignores that the threshold property is only approximately captured by the small-signal model of the neuron.

An alternative approach is to rely on the sharp separation of time-scales observed in neurophysiological models. This time-scale separation was acknowledged since the early experimental work of Hodgkin and Huxley, who immediately recognized the value of separating the *early* current from the *late* current in dissecting the role of intrinsic conductances. In neurophysiology, the capacitive current is regarded as *instantaneous*, the sodium activation is regarded as *fast*, and both the potassium activation and sodium inactivation are regarded as *slow*.

The sharp time-scale separation allows for a quasi-static approximation of the conductances in distinct time scales. We illustrate this decomposition in Hodgkin-Huxley model.

The instantaneous approximation neglects the capacitive dynamics ($C = 0$) and freezes the gating variables to their initial equilibrium conditions. The resulting instantaneous conductance is $g_{\rm tot}$, which is the total quasi-static conductance of the neuron when the frozen gating variables are treated as parameters. The fast approximation neglects both the capacitive dynamics $C = 0$ and sodium activation ($\tau_m = 0$), but freezes the gating variables h and n, adding the contribution of the fast conductance

$$g_f(V) = \bar{g}_{\rm Na} 3m^2(V) m'_\infty(V) h (V - E_{\rm Na}) \qquad (10)$$

where h is a constant parameter frozen at the equilibrium value $h_\infty(V_{eq})$. Finally, the slow approximation considers the total static approximation of the neuronal model, adding the contribution of the slow conductance

$$\begin{array}{rl} g_s(V) & = \bar{g}_{\rm Na}(3m^2(V)m'_\infty(V)(h_\infty(V) - h) + \\ & + m_\infty^3(V)h'_\infty(V))(V - E_{\rm Na}) + \bar{g}_{\rm K} 4 n_\infty^3(V) n'_\infty(V) \end{array} \qquad (11)$$

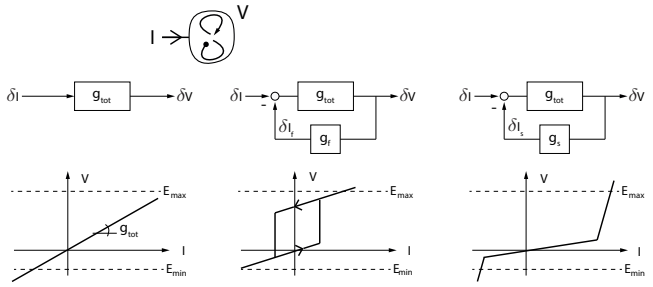

Fig. 3. The mixed-feedback representation of an excitable model : positive feedback in the fast time-scale, negative feedback in the slow time-scale.

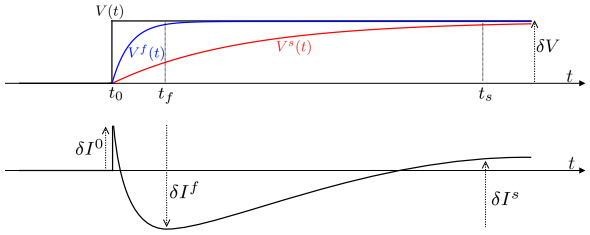

Fig. 4. The current response of an excitable neuron to a voltage step ΔV around a voltage V close to threshold provides an approximation of the three quantities $g_{\rm tot}(V) \approx \frac{\Delta I^0}{\Delta V}$, $g_f(V) \approx \frac{\Delta I^f}{\Delta V}$, and $g_s(V) \approx \frac{\Delta I^s}{\Delta V}$.

This decomposition of the total differential conductance into the sum of an instantaneous, fast, and slow conductances is very useful to understand the role of the intrinsic conductances in shaping the loop-gain of an excitable model. The instantaneous model of the neuron is a passive resistor with open-loop gain $R_{tot} = \frac{1}{g_{\rm tot}}$. The fast conductance provides fast positive feedback amplification as the sign of $g_f(V)$ is always negative. As a consequence of this positive feedback loop, the I-V curve has a range of negative differential conductance in the fast time-scale of sodium activation. For that reason, the fast positive feedback is the source of a *fast* threshold. The slow conductance provides slow negative feedback amplification as the sign of $g_s(V)$ is always positive. The negative feedback loop is the source of refractoriness in the slow time-scale of potassium activation, restoring the monotonicity of the I-V curve and allowing for the slow repolarization of the neuron to its equilibrium value.

The mixed-feedback representation of the neuronal model in Figure 3 is not specific to Hodgkin-Huxley model. It is a central motif of neuronal excitability.

Figure 4 illustrates how the instantaneous, fast, and slow differential conductances of a neuron can be determined from the current step response to a small voltage variation $V+\Delta V$. This experiment is called a voltage-clamp experiment as the voltage is clamped to a prescribed value by an external feedback amplifier. By repeating this experiment for different voltages, one can obtain the differential conductances curves $g_{\rm tot}(V)$, $g_f(V)$, and $g_s(V)$ from input-output data. It is through a series of voltage-clamp experiments that Hodgkin and Huxley identified their model. For a more detailed description of dynamic conductances and how they can be determined analytically or experimentally, the reader is referred to [12].

IV. Neuromodulation of Excitability

A. Excitability is modulated

The excitable behavior of any neuron is made of action potentials, or *spikes*. And every spike is generated by the mechanism described in Section III-C : fast positive feedback amplification followed by slow negative feedback amplification. But this does not mean that every neuron has the same electrophysiological signature. Instead, the neuronal activity comes in a great variety in different neurons. Even more importantly, the same neuron can exhibit different firing modes or *states* depending on the environment. Neuromodulation plays a critical role in controlling the transition between such states.

As early as in 1948, before the 1952 model, Hodgkin distinguished between three classes of excitability on the basis of spiking patterns observed in crustacean axons [28]. Type I axons were capable of spiking repetitively across a broad range of rates (5-150 spikes/s) in proportion to the stimulus intensity. Type II axons were also capable of spiking repetitively but across a narrower range (75-150 spikes/s). In particular, they could not spike at a regular slow frequency. Type III axons were not capable of sustained periodic spiking. This early classification is still used today and has generated a great amount of experimental and modeling papers.

Another classical type of classification is between spiking and bursting. Bursts are discrete events composed of high-frequency trains of spikes interspaced by long inter-burst intervals without spikes. Bursts also come in many forms. Their classification has been the source of a vast literature.

Classifying firing patterns has proven difficult, both for neurophysiologists and for mathematicians.

The neurophysiologist likes to associate different firing patterns to different types of intrinsic conductances. Experiments often consist in asserting the role of a particular conductance by blocking its activation pharmacologically. Such experimental sensitivity analysis can be fragile because the outcome of blocking one type of conductance is sometimes highly dependent of many other conductances. The reader is referred to [14] for a further discussion about the fragility of sensitivity analysis in the presence of many redundant intrinsic conductances.

The mathematician likes to associate different firing patterns to different mathematical models or to different bifurcations in a same mathematical model. Because of the complexity of high-dimensional models that include many different conductances, this analysis is often confined to low-dimensional models that are not easily connected to the neurophysiology. It makes it challenging to relate the role of a neuromodulator to a particular bifurcation parameter.

Efforts to classify firing patterns has led to an increasing divide between experimental neurophysiology and mathematical neuroscience. Conductance-based classification has led to contradictory experimental and/or numerical obser-

vations in high-dimensional models of apparent daunting complexity for the mathematician. Bifurcation-based classification has led to a diversity of mathematical models that are technically challenging and difficult to relate to concrete physiological mechanisms or experiments.

The perspective of neuromodulation offers an opportunity to resolve this divide. It constrains mathematical modeling with the requirements of robustness and modulation. Classification only requires that a mathematical model reproduces a particular type of attractor with a particular set of parameters. This task is daunting in a high-dimensional set of nonlinear differential equations and combinatorial in the dimension of the parameter space. Neuromodulation constrains a mathematical model to exhibit robust modulatory paths in the parameter space. The model must account for the continuous deformation from one attractor into another attractor in the parameter space of maximal conductances. Morover, this continuous deformation must be robust to uncertainty in the remaining model parameters to account for the large variability observed in nature. As further illustrated in Section V, neurons may exhibit the same neuromodulation properties in spite of vastly different conductances.

Constraining a mathematical model to combine robustness and modulation properties is highly discriminant and a very task of control theory. This is why input-output and loop-shaping paradigms are necessary in addition to state-space models of a neuron. The next section will illustrate how elementary loop-shaping ideas can help understanding key modulation mechanisms at the single cell level.

B. Fast and slow excitability

A key insight into the question of neuromodulation comes from the excitability motif discussed in Section III-C. The combination of fast positive and slow negative feedback localizes a range of ultra-sensitivity both in amplitude and in time. The threshold amplitude is localized in a range of a few mV around -55mV whereas the full voltage range of the neuronal voltage exceeds 100 mV. The duration of a spike is a few ms whereas firing patterns extend over hundreds of ms. This localization is primarily determined by the kinetics of sodium activation, which only provides positive feedback in a narrow temporal and voltage range. In short, sodium channels determine the scale of *fast* excitability and the possibility of spiking.

Much of the modulation of the neuronal activity comes from replicating the same excitability motif in a slower time-scale and a lower voltage range, with the help of additional intrinsic conductances. In particular, calcium channels activate very much in the same way as sodium channels, but in a significantly slower time scale. They provide *slow* positive feedback amplification, that is, positive feedback amplification with an activation time-constant that is 5 to 10 times bigger than the activation time-constant of sodium channels. Calcium channels come in great varieties and allow for considerable tuning of the temporal and amplitude range of slow excitability. For instance, T-type calcium channels are frequently associated to neurons that exhibit continuous transitions between spiking and bursting. They are characterized by a *slow* time-scale and a *low* voltage range of activation *relative to* sodium activation. Because of those properties, they can create a second threshold around -65 mV and with the longer latency characteristic of burst initiation or slow spiking. The *slow* positive feedback provided by calcium channels is balanced by *ultra-slow* negative feedback provided for instance by calcium-activated potassium channels. Those channels are similar to the potassium channels of Hodgkin-Huxley model, but their activation can be much slower (e.g. 200-300 ms) and is dependent on the intra-cellular calcium concentration rather than the voltage amplitude.

Slow excitability does replicate the motif of fast excitability but in a distinct amplitude and temporal scale. Four distinct types of intrinsic conductances are necessary to provide the four feedback amplifiers that define fast and slow excitability but many more conductances can contribute to tune this balance of feedbacks in specific temporal and voltage ranges. In nature, the channels that provide positive feedback seem few and attached to specific time scales. Sodium activation is the main contributor of fast positive feedback, and calcium activation is the main contributor of slow positive feedback. But slow positive feedback is also provided by the slow inactivation of fast potassium channels. This is a distinctive role of the A-type potassium current first highlighted by Connors and Stevens [5] to explain Type I excitability. Most potassium currents primarily contribute to negative feedback amplification through their activation variable. Potassium currents come in great variety and their activation covers a broad range of time scales and voltages. The variety of channels encountered in nature matches the view that only two localised negative conductances are needed to define fast and slow excitability but that a continuum of positive conductances allows to continuously deform the spiking and bursting activity of neurons.

C. Control by balancing the gains of four feedback loops

Conceptually, it is not difficult to imagine the modulation capabilities of a neuronal model with two distinct sources of excitability. Fast excitability accounts for the fast time-scale of spiking whereas slow excitability accounts for the slow time-scale of first-spike latency and burst excitability. The combination of fast and slow excitability accounts for bursting and the modulation between spiking and bursting or between different types of bursting.

The view of a neuron as a feedback control system regulated by two positive and two negative feedback loops that balance each other to localize two thresholds in narrow amplitude and temporal ranges is illustrated in Figure 5. Each threshold defines a discrete state that can be turned on (1) and off (0). The resting state has no threshold (00). The spiking state has a fast threshold but no slow threshold (10). The bursting state has a fast and a slow threshold (11). The slow oscillatory state has a slow threshold but not fast threshold (01). This last state is not physiological but such *slow oscillatory potentials* (SOPs) have been reported

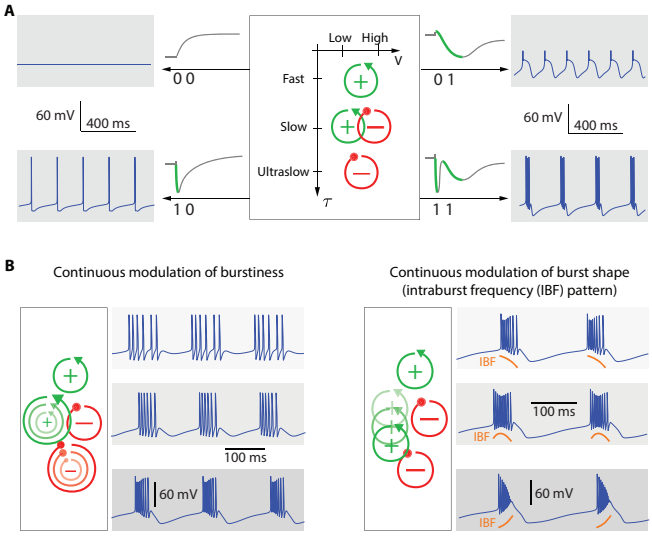

Fig. 5. A. The double mixed-feedback motif of a neuron. The on (1) or off (0) state of each of the two thresholds define four discrete states for the neuron : resting state (00), spiking state (10), bursting state (11), and slow oscillatory state (01). The figure also illustrates the corresponding current response of a volage-clamp step perturbation in the threshold voltage range. Both the fast and slow thresholds have a distinct negative conductance signature in their respective time scales. B. An illustration of how modulating the feedback gains of a neuron can tune the bursting attractor. (Left) Stronger gains in the feedback loops that control slow excitability increase the burstiness of the attractor : the fast and slow excitability properties of the attractor become increasingly decoupled. (Right) Modulating the amplitude range of the slow positive feedback gain modulates how the intra-burst frequency evolves during the slow oscillation of the burst. The three illustrated bursters are reminiscent of have been called square-waved, parabolic, and triangular in the neurodynamics literature.

in many experiments that block the activation of sodium channels.

Both the fast and slow thresholds have a distinct negative conductance signature in their respective time scales and voltage ranges. Those signatures have a robust input-output representation in the dynamic conductances defined in Section III-D. This input-output representation of the neuron is independent of any state-space model. The dynamic conductances are shaped by the intrinsic conductances, that is, by the gains of the feedback amplifiers of the neuronal model. The positive feedback loops shape the ranges of negative conductance and localize the thresholds. The negative feedback loops shape the ranges of positive conductance and tune the refractory periods of spikes and bursts.

From a mathematical viewpoint, a key question is to relate the loop-shaping of dynamic conductances to the attractors of corresponding dynamical state-space models. This question is not discussed in details in the present paper but is addressed in the papers [19] and [20] in the mathematical language of singularity theory and geometric singular perturbation theory. The hysteresis singularity is shown to organize the one-treshold motif of fast excitability, whereas the cusp singularity is shown to organize the two-threshold excitability of fast-slow excitability. The discrete states of the neuronal model are separated by transition varieties in the space of unfolding parameters. There is a remarkable match between the unfolding parameters of singularity theory and the maximal conductance parameters of the four feedback loops of the two-threshold excitability motif. This classification is achieved in the singular limit of a three-time scale model with strong separation between the fast, slow, and ultra-slow time scales. This classification is simple in that it ignores many bifurcations that occur away from this singular limit. Our ansatz is that the simplicity of this classification matches the robustness of attractors that are insensitive to most model parameters of high-dimensional state-space realizations.

From a neurophysiological viewpoint, the control perspective suggests that a specific type of ion channels or neuromodulator contributes to the firing pattern of the neuron insofar that it affects the balance of a few feedback gains. Dynamic conductances provide a bridge between the low-dimensional space of the four feedback gains that shape the conductances and the high-dimensional space of maximal conductance parameters. The excitability thresholds are identified from local properties of the dynamic conductances, and the sensitivity of dynamic conductances to a specific neurophysiological parameter can be easily assessed from a detailed conductance-based model. This analysis is detailed in the papers [10], [12], and [21].

We provide a tutorial illustration in the two next sections.

D. Spiking-bursting modulation in a neuromorphic circuit

The continuous modulation of a neuron between a spiking mode and a bursting mode has been described in many neurophysiological experiments. We will return to the physiological significance of such a transition in Section VII. Here, we reproduce this transition in an artificial neuromorphic circuit studied in [59]. The circuit uses the general architecture in Example 3 and is shown in Figure 6. The four active elements of the circuit match the four feedback gains of the double mixed-feedback motif in Figure 5. We assume that the fast negative conductance element $i_f^-(V)$ is instantaneous. The circuit admits a three-dimensional state-space representation. The model consists of the electrical equation

$$C\dot{V} = -i_p(V) - i_f^-(V) - i_s^+(V_s) - i_s^-(V_s) - i_{us}^+(V_{us}),$$

the slow lag $\tau_s \dot{V}_s = -V_s + V$, and the ultra-slow lag $\tau_s \dot{V}_{us} = -V_{us} + V$. The dynamic conductances of the model take a simple expression: the *fast* dynamic conductance $g_f(V) = \frac{di_f^-}{dV}(V)$ is by definition always negative. The *slow* dynamic conductance is $g_s(V) = \frac{di_s^-}{dV}(V) + \frac{di_s^+}{dV}(V)$, the sum of two conductances of opposite signs. The *ultra-slow* dynamic conductance $g_{us}(V) = \frac{di_{us}^+}{dV}(V)$ is always positive.

The four dynamical conductances of the circuit shape the loop-gain of the feedback system in the three time-scales. In [59], the behavior of the circuit is predicted solely from the shapes of the fast, slow, and ultra-slow I-V curves. The ultra-slow I-V curve includes all currents. The slow I-V curve excludes the ultra-slow current. The fast I-V curve excludes both the slow and ultra-slow currents. The fast and slow thresholds are controlled by a range of negative

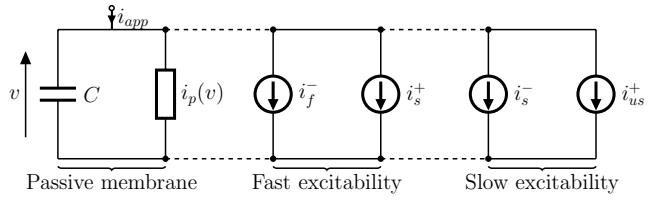

Fig. 6. The neuromorphic circuit of a neuron with four active current sources to match the four feedback gains of the double mixed-feedback motif.

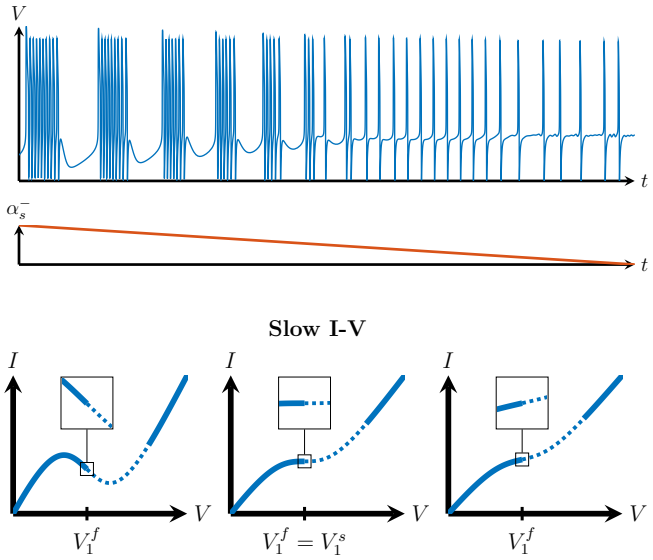

Fig. 7. Continuous transition from bursting to spiking in the neuromorphic circuit of Figure 6 by decreasing the maximal gain α_s^- of the slow negative conductance current $i_s^-(V)$. Adapted from [59].

conductance in the fast and slow I-V curves, respectively. A spiking attractor only requires a fast threshold, meaning an N-shaped fast I-V curve, but a monotone slow and ultra-slow I-V curves. A bursting attractor requires both a fast and a slow threshold, meaning N-shaped fast and slow I-V curves, and a monotone ultra-slow I-V curve.

Figure 7 illustrates a simple control mechanism for spike-bursting modulation in this circuit. Only the gain of the slow negative conductance is modulated to control the monotonicity properties of the slow I-V curve. The initial gain is strong enough to create a range of negative conductance in the slow I-V curve, resulting in a bursting attractor. The gain is continuously decreased and eventually makes the slow I-V curve monotone, resulting in a spiking attractor. Although the circuit model is highly simplified with respect to detailed neurophysiological models, it captures an important important property: intrinsic conductances that contribute to the slow negative conductance of the neuron play a critical role in the control of bursting and slow spiking. This property is further illustrated in the next section.

E. Excitability modulation in Connors-Stevens model

The work of Connors and Stevens [5] in the early 70's is an early demonstration that particular intrinsic conductances can control the excitability of a physiological neuron. Through a series of voltage-clamp experiments in a (gastropod) neuron, the authors isolated two distinct types of potassium currents: a potassium current I_K with slow activation (and no inactivation), similar to the potassium current of Hodgkin and Huxley model, and a potassium current I_A with *fast* activation and *slow* inactivation. They showed that a model including a current I_A in addition to the two currents I_{Na} and I_K of Hodgkin-Huxley model could exhibit arbitrarily slow firing. In the 1948 classification of Hodgkin, Connors-Stevens model is a model of Type I excitability whereas Hogdkin-Huxley model is a model of Type II excitability.

Connors-Stevens model was recently revisited in [15] to clarify the role of the current I_A from a loop-shaping perspective. Through its slow inactivation, the current I_A is a source of slow negative conductance. Hence its inactivation contributes to the slow positive feedback amplification of the circuit, or, equivalently, to shaping the negative range of the slow dynamic conductance. This is counter-intuitive because the potassium current is an outward current. The static conductance of an outward current is always positive. But transiently, it can contribute to positive feedback amplification in the same way as the slow activation of an inward current (like calcium). The two currents I_K and I_A contribute to the slow dynamic conductance of the neuron in the same way as the currents i_s^+ and i_s^- in the neuromorphic circuit of the previous section : through its slow activation, I_K contributes to the slow *positive* conductance of the neuron; through its slow inactivation, I_A contributes to the slow *negative* conductance of the neuron. Both currents can balance each other to result in a range of nearly zero conductance like in the middle I-V curve of Figure 7. As explained in [15], a nearly zero conductance is the very impedance property required for long interspikes intervals.

The dynamical conductance analysis in [15] resolves a number of puzzling experimental and modeling paradoxes associated to the role of the I_A current. For instance, Connors and Stevens showed that the current I_A could control a transition from Type II to Type I excitability, but other experiments conducted on other neuron types concluded that I_A currents could instead favor a transition from Type II to Type I. A dynamic condutance analysis shows that the type of transition is determined by the relationship between I_A current kinetics and the kinetics of other currents: if I_A inactivation is slow as compared to sodium current activation, the channel provides a source of slow negative conductance and promotes a transition from Type II to Type I excitability. If instead the I_A activation is slow as compared to sodium current activation, then its inactivation becomes ultraslow. In that case, the channel contributes to the slow *positive* conductance and promotes a transition from Type I to Type II. Many examples of both situations can be found in the experimental literature (see e.g. Fig. 6 of [15]).

V. Homeostasis, regulation and dysregulation

For a neuron to maintain a specific conductance profile, ion channels need to be synthesized and expressed at appro-

priate levels in the membrane. This is a dynamic process. The lifetime of an individual ion channel is of the order of hours or days [47], while its dwell-time at the membrane where it contributes a conductance may be shorter. The fact that channels are continually synthesized and broken down implies that some form of cellular feedback control must exist to maintain a stable net conductance density [58], [47].

Widespread experimental evidence supports the existence of internal cellular mechanisms that sense ongoing voltage fluctuations and exert negative feedback control to maintain stable conductance densities. These feedback mechanisms are found to compensate for external perturbations to neurons that change average input over extended periods. For example, if neurons are artificially depolarized for many hours, the conductance densities and therefore the excitable behaviour adapts to make the neuron less excitable [55]. Conversely, a long-lived reduction in the amount of excitatory input that a neuron receives results in a net increase in the neuron's intrinsic excitability [8]. Existing theoretical models attempt to capture this kind of regulation and explore its consequences for neural circuits [4], [56], [57], [42], [39]. In fact, the existence of such a feedback mechanism was hypothesized before it was shown experimentally [39].

Several models of ion channel regulation [4], [56], [57], [42], [39] assume, in line with experimental evidence, that ion channel densities are controlled using intracellular calcium concentration as a feedback signal. Calcium tracks membrane potential fluctuations due to the existence of voltage gated calcium channels that operate over a wide range of membrane potentials. In turn, a host of calcium sensitive enzymes transduces this signal into changes in the density of channels at the membrane via a number of mechanisms that are still poorly understood.

A recent model [57], hypothesizes that (approximate) integral feedback control is employed to maintain intracellular calcium c at a nominal reference concentration c_T:

$$\begin{cases} \tau_m \dot{m} = c_T - c \\ \tau_g \dot{g} = m - g \end{cases}$$

where g represents the maximal conductance, or conductance density of a particular channel type, m is the corresponding channel precursor, or mRNA. The implicit assumption in these models is that neurons use calcium concentration as a proxy for neural activity. The timeconstants, τ_m, τ_g are assumed to be *several orders of magnitude longer* than the slowest timeconstant in the membrane potential dynamics of the neuron. This timescale separation means that the controller maintains calcium concentration at the nominal concentration *on average*. This is important because membrane potential fluctuations are necessary for neuronal signalling.

There are several complicating factors that neurons must have overcome to achieve reliable function. We will focus on two of these:

1) ion channel degeneracy
2) reliable neuromodulation

There is a large degree of degeneracy in the kinds of ion channels expressed in many neurons and excitable cells. For example, the human genome contains 40 known voltage-gated potassium channel genes. Each gene typically encodes multiple versions of a protein subunit that is in turn combined with other subunits to make ion channels, resulting in a surprisingly large array of *ion channel types*. The biophysical properties (such as voltage dependence, ion selectivity, gating dynamics) of these channel types might differ substantially, or somewhat subtly. They provide a large number of redundant degrees of freedom for controlling neuronal excitability [23].

For concreteness, we can express this degeneracy in the notation we introduced above. Recall the decomposition of membrane conductances:

$$C\dot{V} = -i_p(V) - i_f^-(V) - i_s^+(V_s) - i_s^-(V_s) - i_{us}^+(V_{us}).$$

Let us enumerate these dynamic conductances using an index, $j \in \{1, ..., 5\}$ so that $i_1(V) := -i_p(V), i_2(V) := -i_f^-(V), ...$ and so on. Now denote the contribution of N individual ion channel types by $\{\tilde{i}_k(V)\}_{k=0}^N$. Under the assumption that dynamic conductances capture the behaviour of a neuron, we have

$$C\dot{V} = \sum_j i_j(V) = \sum_k \tilde{i}_k(V).$$

Generically $N >> 5$ and we therefore have a degenerate mapping between the ion channel type and the dynamic conductances,

$$\mathbf{i}(V) = \mathbf{W}(V)\tilde{\mathbf{i}}(V)$$

for an appropriately chosen weighting matrix, $\mathbf{W}(V) = \{w(V)\}_{jk}$. This degeneracy matters because neurons control their conductance properties by controlling the expression of genes that encode ion channels. Any effective regulation mechanism must therefore implicitly take into account this degenerate mapping.

A consequence of ion channel degeneracy is that it permits variability in the expression of ion channels in neurons. This is in fact seen in experimental data: repeated measurements of the abundances of ion channel channel genes show several-fold variation in channel expression in the same neuron class [24], [61], [62]. It remains an open question whether channel regulation mechanisms impose specific constraints on channel expression beyond those induced by a simple feedback regulation of the form described above.

One potential drawback of degenerate channel expression is the danger that variable channel density leads to unreliable neuromodulatory responses. This is illustrated in Figure 8. To achieve reliable neuromodulation, channel densities need to be tuned such that the modulated state corresponds to an appropriate physiological behaviour. These dual requirements - nominal physiological behaviour and nominal modulatory response - imply the existence of feedback mechanisms that sense the physiological state of a neuron and control ion channel expression to maintain that state.

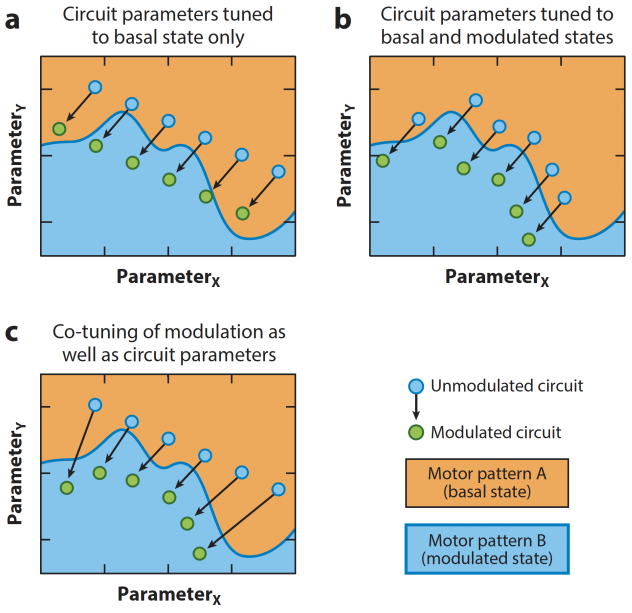

Fig. 8. Channel expression variability poses a problem for reliable neuromodulation. Figure reproduced from [49].

At present, there is no experimentally identified mechanism for achieving this tuning. It is possible that cellular signals that transduce the modulatory signal themselves interact with feedback mechanisms to fine-tune channel expression. It is also possible that cellular sensors of ongoing neural activity feed back on the release of neuromodulators to ensure appropriate switches in activity. In either case, it is also clear than none of these mechanisms are perfectly reliable. Neurons and nervous systems as a whole are not capable of compensating for many kinds of perturbations to channel expression, or environmental perturbations that alter channel physiology [54]. These failure modes may provide further clues as to how modulation and homeostasis interact.

VI. Cellular neuromodulation for rhythmic circuit control

So far, we have focused our attention on the neuromodulation and homeostasis properties of a single cell. In the last part of this tutorial, we illustrate how the neuromodulation of cellular properties provides control principles for circuits and synchrony mechanisms for possibly large and heterogeneous populations.

A. Cellular control of an I-I circuit

The I-I motif is central to the circuit neurophysiology of central pattern generators [46]. It is arguably the most elementary and most comprehensively studied neuronal circuit. It consists of two bursting neurons reciprocally interconnected with inhibitory synaptic conductances that activate in the slow or ultraslow time scale of neuronal excitability. Even if the neurons do not endogeneously burst in isolation, an endogenous circuit anti-phase rhythm emerges from interconnecting the two cells.

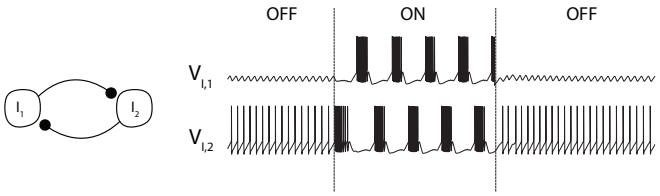

Fig. 9. The influence of the nodal mode of excitability on the basic I-I motif. The motif defines a behavior at the circuit scale distinct from the behavior at a nodal scale. The circuit behavior is turned on and off by modulating the excitability mode of the nodes. Adapted from [65].

Conceptually, the rhythmic nature of the circuit is simple to understand : A burst in neuron I_1 induces a hyperpolarizing synaptic current into neuron I_2. The termination of a burst in neuron I_1 acts as a depolarizing step input, eliciting a burst in neuron I_2. The reciprocal interconnection from neuron I_2 to neuron I_1 closes a network loop that can sustain an autonomous anti-phase rhythm in the circuit. This circuit oscillation is illustrated in the 'on' phase of Figure 9. It is turned off in the 'off' phase of the figure. The on-off control of the circuit rhythm is the neuromodulation of the slow intrinsic negative conductance of any of the two neurons. In the absence of slow positive feedback amplification, the neurons become spike excitable rather than burst excitable. This modulation from burst excitability to spike excitability disconnects the neuron from the circuit by strongly reducing the synaptic drive from neuron I_2 to neuron I_1.

This simple neuromodulation control mechanism is significant because it provides a cellular switch for the circuit rhythm. The 'on' mode is a circuit behavior. The circuit rhythm is defined by a robust phase arrangement of the cellular bursts. Only the phase arrangement is dictated by the circuit connectivity. The 'off' mode is a cellular behavior: each cell in the 'off' mode becomes functionally disconnected from the circuit because only the synaptic drive of bursts is sufficient to couple the cellular behaviors.

The neuromodulatory control illustrated in Figure 9 is robust to parameter heterogeneity. The reader is referred to [12] for an extensive investigation of the robustness of the circuit rhythm in the parameter space of both intrinsic and synaptic conductances. In the 'on' mode, the circuit rhythm persists over a broad range of parameters, allowing for asymmetric coupling between heterogenous neurons. This robustness of the control to parameter variations is what allows a continuous tuning of circuit oscillation properties such as frequency or duty cycle. In contrast, a circuit rhythm in the 'off' mode is difficult to observe and highly non generic. It requires careful tuning of the parameters and, in particular, a precise relationship between intrinsic (cellular) parameters and synaptic (connectivity) parameters. The resulting rhythm is rigid, that is, lacks tunability properties, and it is also fragile to any parameter variations. No circuit rhythm exists in the 'off' mode.

B. Cellular control of a central pattern generator

The neuromodulatory cellular control of the I-I motif provides a versatile control principle for circuits composed

of excitable nodes interconnected by inhibitory synaptic currents. In neurophysiology, such circuits have long been associated to rhythmic functions such as breathing, chewing, swallowing, walking or heart beating [25], [26], [41], [34]. We will briefly illustrate how nodal control shapes the behavior of the five-node circuit illustrated in Figure 10. We refer the interested reader to [13] for a detailed analysis of the circuit. The circuit architecture is inspired by the neuronal topology of the crab somatogastric ganglion (STG), which has served as a key experimental model to study the neuromodulation of rhythmic circuits over the past forty years [45]. In experiments, two different rhythms coexist within the STG circuit. One corresponds to the fast pyloric rhythm, which is constantly active, whereas the second corresponds to the slow gastric mill rhythm, which can be turned on and off by afferent neuromodulatory inputs and neuromodulators. Each node in the circuit is a conductance-based model that includes seven different types of nodal currents. Those currents are not discussed in detail here but their conductances can be shown to shape the four feedback amplifiers of an endogeneously bursting neuron. In particular, the model includes two calcium currents that provide the critical source of slow negative conductance necessary for burst excitability. Our control parameter is the maximal conductance of those two currents, that can modulate the nodal excitability of each node between the two modes of excitability. The topology of the network is indicated in Figure 10. It includes passive currents between nodes 2, 3, and 4, and a number of inhibitory synaptic currents with slow and ultraslow activation. Reciprocal inhibitory connections between nodes 1 and 2 and between 4 and 5 define two elementary I-I motifs, one for the fast rhythm between nodes 1 and 2, one for the slow rhythm between nodes 4 and 5. The two distinct I-I motifs interact through the central node 3.

The figure illustrates the different rhythms that can coexist in the circuit by controlling the excitability mode of the nodes. The significance of this nodal control is that the interconnections gains (and in particular the maximal conductances of the synaptic currents) are kept unchanged in the five circuit rhythms shown in Figure 10. The circuit behavior is modulated by nodal control rather than by network control. Nodal control modulates the functional connectivity of the network without changing the synaptic connectivity. The circuit behavior is easily inferred from the I-I motif behavior because the circuit topology only orchestrates the phase relationships between discrete events defined at a smaller scale.

Although the circuit in Figure 10 is a highly simplified cartoon of the physiological STG circuit, the robustness and tunability of the proposed neuromodulatory control principle provide a biologically plausible hypothesis. The recent experimental investigation in [60] adds further biological plausibility by discussing two distinct neuromodulatory mechanisms that produce similar changes in the circuit connectivity. Consistently with our proposed analysis, the voltage clamp experiments reported in the paper illustrate

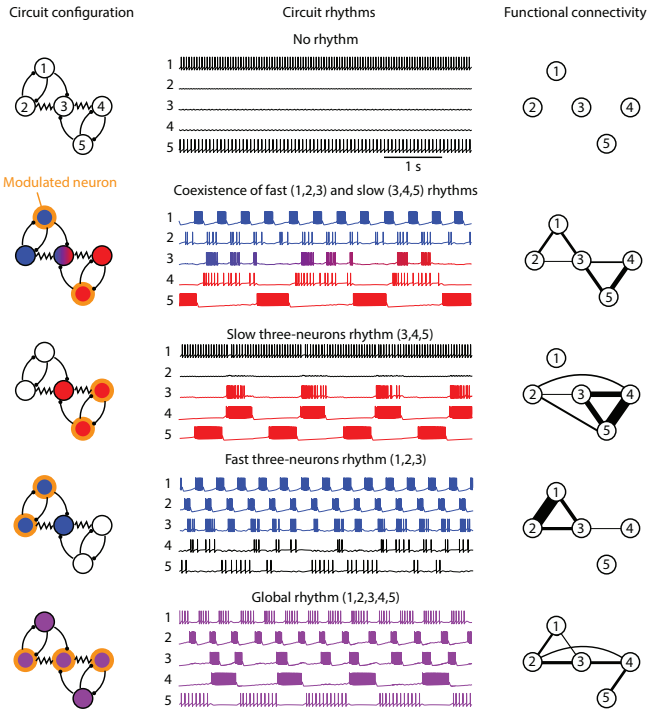

Fig. 10. Nodal control of a circuit behavior with a fixed synaptic connectivity. Left, circuit connectivity diagrams. Filled circles represent neurons, which are numbered from 1 to 5. Neurons with thick orange edges are controlled by neuromodulatory inputs that increase the maximal conductance of calcium currents. Center, membrane potential variations over time for neurons 1 to 5 (from top to bottom) in the different control configurations. Synaptic connections are identical in all cases. Neurons are colored in blue when they participate in the fast rhythm, in red when they participate in the slow rhythm, in purple when they participate in a global rhythm, and in black when they do not participate in the circuit rhythm. Right, functional connectome in the different control configurations. Adapted from [13]

that both neuromodulatory mechanisms modulate intrinsic slow negative conductances of the STG circuit.

VII. Cellular Neuromodulation for Network Control

A. Cellular control of an E-I circuit

The E-I motif is another central circuit of neurophysiology. The circuit consists of two neurons interconnected by a fast excitatory synapse and a slow inhibitory synapse. As illustrated in Figure 11, the E-I circuit exhibits a ‘on’ and a ‘off’ modes analogously to the I-I circuit. The control mechanism is however different. In the I-I circuit, the control is through the modulation of the intrinsic slow conductance of the neuron. It involves neuromodulators that change the balance between ion channels providing positive and negative feedback in the slow time scale of excitability. In the E-I circuit, the control is through the modulation of the membrane equilibrium potential. It involves neuromodulators that change the static balance between inward and outward currents. Control of the I-I circuit necessarily involves the modulation of intrinsic conductances, whereas control of the E-I circuit can be achieved by modulation of either intrinsic or synaptic conductances. In contrast, the modulation of the

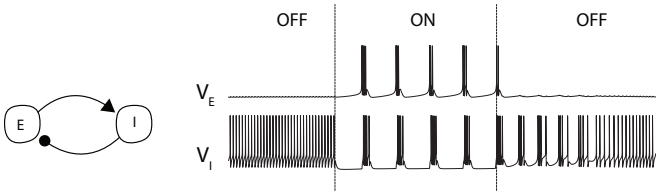

Fig. 11. The cellular ('off') mode and the circuit ('on') mode of a E-I circuit. The control mechanism specifically requires a T-type calcium channel to ensure spike excitability in a depolarized membrane and burst excitability in a hyperpolarized membrane. The switch between the two modes is then controlled by any neuromodulator that modulates the membrane polarization. Adapted from [65].

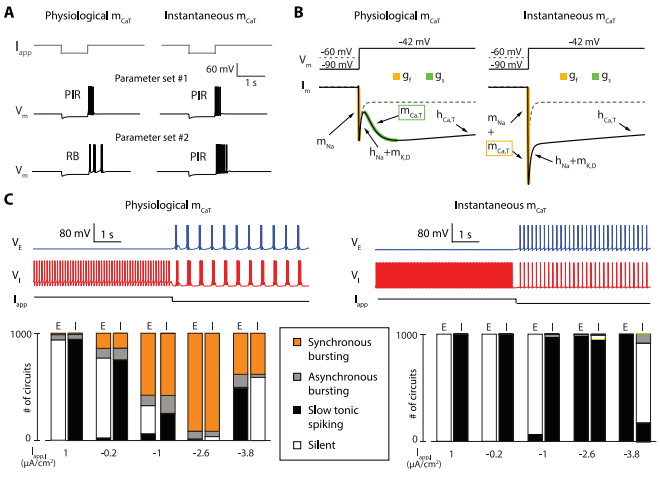

Fig. 12. A robust network switch that is compatible with global neuromodulation, synaptic plasticity and homeostasis. Adapted from [11].

E-I circuit specifically requires an intrinsic negative conductance that only activates at low potentials. This is the property that makes the neuron spike excitable by depolarization and bursting by hyperpolarization. In neurophysiology, slow activation in a low-voltage range is a defining characteristic of T-type calcium channels, also known as low-threshold calcium channels. The role of T-type calcium channels has been emphasized in important sensorimotor circuits including the relay neurons of thalamocortical-circuits and the neurons of the subthalamic nucleus in the basal ganglia. Those two types of neurons are prime examples of neurons that have been shown to exhibit a continuous transition from bursting to spiking by depolarization.

The control mechanism suggested in Figure 11 is robust. We refer the interested reader to the recent work [11] for a detailed exploration of the robustness of the switch to parameter variations. Control by hyperpolarization was simulated in a thousand different circuits with random perturbations in both intrinsic and synaptic maximal conductances. Figure 12 C illustrates that the switch is observed in the vast majority of networks. This robustness is significant as it decouples the control of the circuit mode from the tuning of the circuit rhythm. The frequency and duty cycle of the circuit oscillation can be modulated without loosing the switching property.

What is also illustrated in the Figure is that this robust switching property depends critically of the *slow* activation of T-type calcium channels. When the simulations are repeated with an instantaneous activation of the channels, the switch is completely lost for *all* generic perturbations of the parameters. This is because the instantaneous activation of the channels eliminates the slow positive feedback loop that is critical to bursting. This is clearly illustrated in the voltage clamp step response shown in Panel B of the figure. The model has no slow negative conductance without the slow activation of T-type calcium channels.

This feedback property is not properly understood in the modeling literature of T-type calcium channels. Many computational studies assume an instantaneous activation, ignoring the consequence of that simplification on the feedback properties of the neuron. The discussion of the E-I and I-I circuit rhythms in the literature is most often in terms of the rebound (RB) or post-inhibitory rebound (PIR) properties of the model. Panel A of the figure shows that the neuron can possess those rebound properties both with slow and instantaneous activation of the T-type calcium channels. Yet only the neurons with slow activation can exhibit a robust switch between spiking and bursting. This misconception illustrates the subtle and sometimes overlooked role of feedback properties in neuronal behaviors.

B. Synchrony in heterogeneous populations

The robustness of the cellular control of the E-I circuit is significant for neuromodulatory control of large populations of neurons. Rhythmic synchrony in large populations is instrumental in defining network states with a clear mean-field signature that can be detected with large electrodes or even EEGs. Such signatures have long been reported as *brain states* that control attention in cortical circuits [50], [51], attention and arousal in the thalamus, and movement initiation in the subthalamic nucleus [37]. The most studied example is probably the thalamo-cortical circuitry. The thalamus acts as a plastic relay between sensory systems, different subcortical areas and the cerebral cortex, by gating and modulating neuronal signal flow under the modulatory effect of cortical feedback [67], [68].

Figure 12 shows that the neuromodulatory control of the E-I circuit provides a robust and versatile control mechanism to control synchrony in large and heterogeneous populations. The 'off' mode of the circuit corresponds to an asynchronous population state with no specific mean-field signature. Instead, the 'on' mode corresponds to a synchronous population state with a clear mean-field signature. The modulation between the asynchronous and the synchronous population states can be fast and accurately controlled spatially because the receptors of each neuron in the population can be tuned to respond or not to the neuromodulator. It is also robust to the heterogeneity of the population: the mean-field neuronal behavior is robustly controlled by the neuromodulator in spite of a variety of different rhythms at the cellular level and in spite of weak synaptic connections. The robustness of this population behavior and its tunability at a cellular resolution

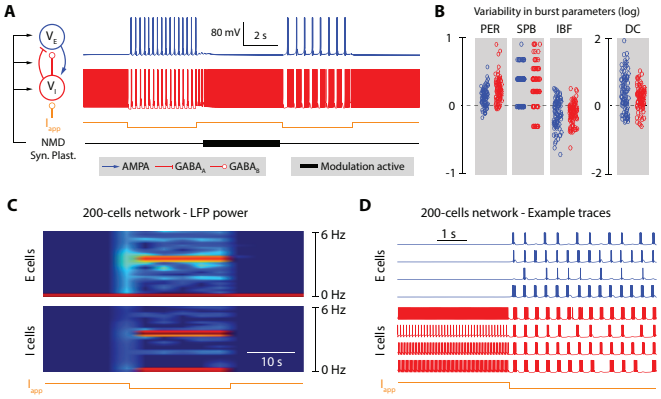

Fig. 13. Neuromodulation controls synchrony in a large population of heterogenous E-I circuits. Adapted from [11].

confer biological plausibility to the proposed neuromodulation mechanism. This mechanism is in sharp contrast with the consensus or synchronization models of control theory. Those models compensate for stronger heterogeneity with stronger coupling. Controlling population synchrony through the sensitivity of nodes rather than through the strength of the coupling is another inspiring lesson of neuromodulation for network control theory.

VIII. Conclusions

Neuromodulation is an important property of physiological neuronal networks. This tutorial has stressed the importance of neuromodulation as a feedback control mechanism. By modulating the maximal gain of intrinsic conductances, neuromodulators shape the loop gain of feedback amplifiers in specific time scales and voltage ranges. In particular they modulate excitability thresholds, which correspond to localised ranges of nearly zero conductance, or, equivalently, of nearly infinite sensitivity. We have shown the importance of both fast and slow thresholds in neuronal excitability. Slow thresholds control the type of excitability and the modulation between spike excitability and burst excitability. This cellular neuromodulation is potentially very important for the robust and versatile control of circuit rhyhtms and synchrony in large populations. Cellular thresholds are feedback properties. They cannot be modulated by the modulation of synaptic conductances.

The modulation of intrinsic conductances has received less attention in the modeling literature than the modulation of synaptic conductances. It requires feedback analysis as opposed to feedforward analysis. Feedback control theory might clarify apparent paradoxes from the experimental or modeling literature with a loop-gain analysis adapted to loop gains that are voltage-dependent and time-scale dependent rather than frequency dependent. This analysis has a close connection to the voltage-clamp analysis of experimental electrophysiology. The concept of dynamic conductances is a step in that direction.

Conversely, a better understanding of neuromodulatory principles is a source of inspiration for engineered circuits or artificial neuronal networks. Neuronal excitability can be understood as a form of localized nodal ultrasensitivity. Modulating nodal sensitivity of nodes by feedback may inspire unexplored avenues in the robust control of networks and in the control of rhythmic circuits. The potential of those ideas for control across scales is further developed in [65].

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