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# Reliable neuromodulation from adaptive control of ion channel expression ⋆

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**Abstract:** Neuromodulation significantly alters neuronal activity and the responsiveness of both neurons and circuits to external inputs by adapting ion channel expression. However, basal ion channel expression is highly variable in neurons, even those with similar functions, which poses the question of how neuromodulation can act reliably. In this paper, we exploit the biophysical structure of neurons and the properties of neuromodulation-induced intracellular signaling to test whether reliable neuromodulation could be achieved by an intracellular control system adapting ion channel expression. The proposed controller has the typical structure of a linear adaptive loop that tunes cellular feedback gains determining neuronal excitability. The feedforward block transforms the neuronal feedback gain reference trajectory into an ion channel expression reference trajectory, while the feedback block, in the form of a simple PI controller, tracks the reference. Both blocks are biologically grounded, yet simple and mathematically tractable. We show that such a simple and biologically grounded control scheme can explain how reliable neuromodulation could be achieved in highly variable neurons. These results illustrate how a complex and highly nonlinear control problem can be tackled by a simple, biologically plausible control loop involving only a few variables.



*Keywords:* Control in neuroscience, Adaptive control, Systems biology

## 1. INTRODUCTION

Cerebral activity is continuously shaped through the action of numerous neuromodulators and neuropeptides such as dopamine, serotonin, and histamine (Bargmann and Marder, 2013; Marder et al., 2014). These molecules dynamically affect the intrinsic properties and activity of single neurons and the strengths and dynamics of synaptic connections, providing means to constantly adapt a neuronal network activity in response to ever-changing needs, contexts, and environments (Marder and Calabrese, 1996; McCormick et al., 2020). Neuromodulators mainly act by changing the density, dynamics, and kinetics of transmembrane ion channels. The signaling of the entire brain therefore strongly depends on the robustness and reliability of neuromodulation actions at the molecular and cellular levels.

Although the ubiquity of neuromodulator action in all nervous systems has been acknowledged several decades ago, the mechanisms underlying their reliable action still remain elusive, particularly because they indirectly target the intrinsic properties of highly heterogeneous neurons (Marder et al., 2014). Neuromodulators act through the activation of metabotropic receptors. These receptors affect ion channels through second messengers that trigger complex and varied signaling cascades, eventually resulting in a wide range of effects depending on the neuron type. Many neuromodulators can target the same subset of ion channels, potentially leading to interfering effect (Marder and Bucher, 2007). Ion channel densities have been shown to be highly variable even in neurons of the same types, sometimes varying up to 5 folds (Schulz et al., 2006). These observations raise the question of how neuromodulators can reliably work at the whole brain level whilst indirectly targeting these variable properties at the molecular and cellular levels.

In this work, we explore how reliable neuromodulation can be achieved through a simple intracellular feedback control system whose reference activity is set by the neuromodulator concentration level. This intracellular control system is motivated by the structure of metabotropic receptor signaling and exploits, rather than being affected by, variability in ion channels density. The resulting adaptive feedback control system is similar to a recently proposed adaptive conductance control system (Schmetterling et al., 2022) but with some key differences. First, the proposed control system is biologically plausible. As such, it provides a new mean to connect biological and engineered neuronal systems. Second, it does not require the knowledge of a reference membrane potential trajectory and to compare this reference trajectory with the neuron membrane potential trajectory. Rather, it exploits the mapping from neuronal intrinsic feedback gains to neuronal behavior (Drion et al., 2015a) to use simpler, *i.e.*, constant, references for those

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gains, which makes sensing and action more parsimonious. Third, the proposed model is fully compatible with existing models of neuronal homeostatic control (O'Leary et al., 2014).

The paper is organized as follows. Section 2 reviews the biology of neuromodulation-mediated neuronal regulation and translates it into an adaptive control scheme. Section 3 translates the derived control scheme into equations, partly relying on dynamic input conductance theory (Drion et al., 2015a). Section 4 presents numerical results and discuss their relevance in terms of reliable neuromodulation. Conclusions and perspective are discussed in Section 5.

## 2. NEURONS AS ADAPTIVE NEUROMODULATION-CONTROLLED SYSTEMS

### *2.1 Neuronal excitability and neuromodulation from an adaptive feedback control perspective*

Excitability is a dynamical property that is fundamental to neurons. Yet intuitive, excitability is mathematically challenging since neurons are nonlinear, often high-dimensional, and their dynamics exhibit complex kinds of attractors, like limit cycles with multiples characteristic timescales. This makes the study of excitability and its modulation often hardly tractable, particularly when using neuron models made of high-dimensional nonlinear systems of ordinary differential equations.

Looking at neuronal excitability as a feedback control system permits to overcome this complexity by merging the effects of the many voltage-gated ion channels into a set of feedback gains acting on a few timescales (Drion et al., 2015a). Neuronal dynamics can indeed be modeled as a control system where many voltage-gated (and some calcium-gated) ion channels define a controller that outputs a control signal $I_{\text{int}}$ to a passive membrane, representing the plant (Drion et al., 2015b) (Fig. 1, blue block).

The controller is tuned by the balance of many different types of ion channels, whose voltage-gating mechanisms can be sources of positive or negative feedback acting on different timescales. In a bursting neuron, the many timescales of channel gating can be merged into three sharply separated timescales, which we call fast, slow, and ultraslow. The feedback actions of all channel variables acting on a similar timescale balance each other to define a voltage-dependent feedback gain in each timescale. Dynamic input conductance (DIC) theory can be used to compute these gains (Drion et al., 2015a). In this way, excitability and its modulation emerge from the balance of positive and negative feedback loops at only three different timescales, which drastically lowers the dimensionality of the problem and makes it amenable to rigorous mathematical analysis through bifurcation and singularity theory (Franci et al., 2019).

The feedback control viewpoint of neuronal dynamics permits to study the mechanisms of reliable neuromodulation in a tractable way. Indeed, the primary targets of neuromodulators are ion channel densities (Marder et al., 2014), which themselves determine the feedback gains of the controller on each timescale. Neuromodulation can thus

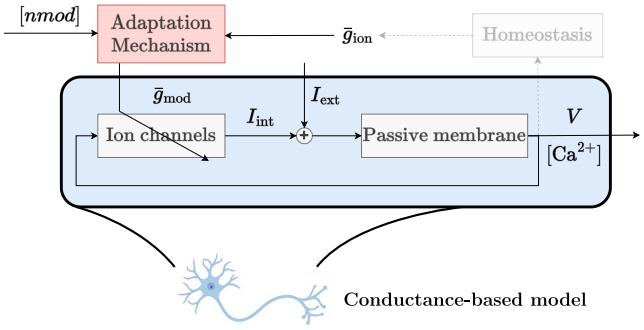


Fig. 1. High level block diagram of the adaptive neuronal controller. The blue block depicts the typical structure of a conductance based model from the feedback control perspective. A neuron is composed of a controller, *i.e.*, voltage and calcium controlled active ion channels, that produces an intrinsic current $I_{\text{int}}$, and a plant, *i.e.*, the passive membrane. *In vitro*, an external current $I_{\text{ext}}$ can also be applied to excite the neuron. The red block lumps all the biological mechanisms that regulate ion channel expression and that act as an adaptive layer onto the neuronal controller. Neuromodulator concentration $[nmod]$ can be modeled as an input to this adaptive block. See text for more details.

be understood as an input to an adaptive control block whose main role is to tune neuron behavior by adapting the feedback gains of the neuronal controller in a functionally relevant way, as depicted in Fig. 1, red block.

The neuromodulatory inputs to the adaptive block represents the neuromodulation concentration in the vicinity of the neuron. The adaptive control layer also receives ion channel expression values $\bar{g}_{\text{ion}}$ as an input. Biologically, this input could be the output of a further neuronal adaptive control block, most naturally, a homeostatic control one (O'Leary et al., 2014), that reads the neuron outputs (membrane potential $V$ and intracellular calcium concentration $[Ca]^{2+}$) and maps them to overall level of ion channel expressions to maintain excitability levels into safe bounds. We omit this block in the present work.

### *2.2 The neuromodulation adaptive control layer*

Using the proposed viewpoint of neuromodulation and exploiting the indirect properties of cell signaling, we derived the adaptation mechanism system of Fig. 2. The proposed adaptation mechanism consists of two blocks: a reference generator block and a reference tracking block, *i.e.* a feedforward block and a feedback block respectively. The outputs of this neuromodulation-dependent adaptive system are ion channel expressions that tune neuronal feedback gains.

The feedforward block represents the activation of a metabotropic receptor that sets a neuromodulation dependent target for neuronal excitability properties by setting a reference signal for the modulated ion channels expression (Fig. 2, blue block). Using DIC theory, setting a target for neuronal excitability properties is equivalent to setting targets, encoded in the vector $g_{\text{DIC}}(V_{\text{th}})$, for the neuron feedback gains at threshold voltage $V_{\text{th}}$ where the neuronal behavior is maximally sensitive. A molecular network,

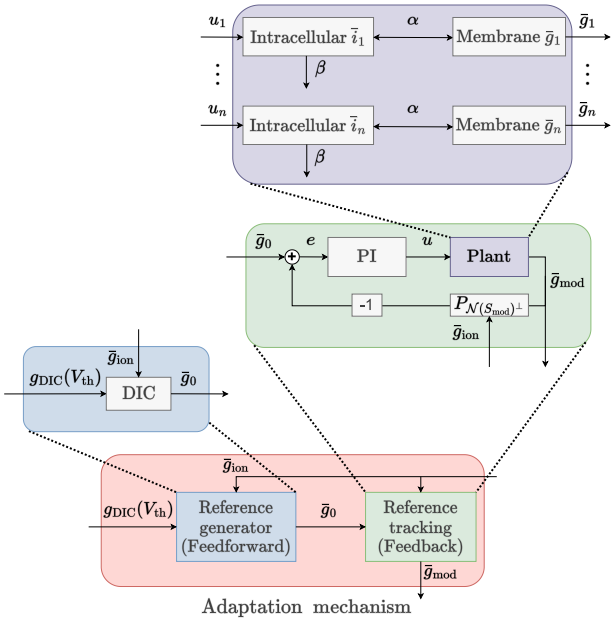


Fig. 2. Detailed block diagram of the adjustment mechanism, red block of Figure 1. It is composed of two sub-blocks: a reference generator (feedforward) block in blue and a reference tracking (feedback) block in green. The feedforward block models a cell signaling cascade that maps target neuronal gains $g_{\mathrm{DIC}}(V_{\mathrm{th}})$ at threshold voltage $V_{\mathrm{th}}$ to a reference signal $\bar{g}_0$ for modulated ion channel expression. The feedback block regulates ion channel expression through a classical PI negative feedback control loop of a molecular plant describing ion channel protein translation, trafficking, and membrane turnover. See text for details.

triggered by the metabotropic receptor activation, maps these target gains into references $\bar{g}_0$ for the modulated channel expressions.

Reference ion channel expression serves as the input of a PI regulated protein translation control system that creates new transmembrane proteins that are transported to the membrane by diffusion or active trafficking (O'Leary et al., 2014). The transport mechanism is modeled using two compartments representing the intracellular and membrane domains. Ion channel movement between the two compartments is modeled by simple passive diffusion, and ion channel turnover is accounted for by introducing a continuous degradation of transmembrane proteins in the intracellular domain (Fig. 2, purple block). For each modulated conductance, a positive translation control signal representing the synthesizing of new transmembrane proteins is computed by a classical negative feedback controller aiming at matching the ion channel conductance to its reference (Fig. 2, green block).

The projection matrix $P_{\mathcal{N}(S_{\mathrm{mod}})^{\perp}}$ appearing in the feedback block is a mathematical abstraction of ion channel degeneracy, meaning that many ion channel combinations can lead to the same excitability type, *i.e.*, the same neuronal gains. Degeneracy can be understood as the existence of a subspace of ion channel expressions in which excitability properties do not change. Only regulation with respect to this subspace is relevant for tuning excitability and this is obtained by projection through $P_{\mathcal{N}(S_{\mathrm{mod}})^{\perp}}$. We derive an expression for $P_{\mathcal{N}(S_{\mathrm{mod}})^{\perp}}$ in the next section. Biologically, a molecule regulatory network can implement the mapping defined by $P_{\mathcal{N}(S_{\mathrm{mod}})^{\perp}}$.

## 3. PUTTING BIOLOGY INTO EQUATIONS

This section is dedicated to put the blocks of Figures 1 and 2 into equations.

### *3.1 Neurons as electrical circuits: the conductance-based framework*

Mathematical modeling of neuronal excitability was pioneered by Hodgkin and Huxley (Hodgkin and Huxley, 1952). Models based on the Hodgkin-Huxley formalism are known as conductance-based models as they represent the neuronal membrane as an equivalent resistor-capacitor circuit. These models are a biophysical representation of an excitable cell in which current flowing across the membrane is split into two quantities: $I_C$ due to charging of the membrane capacitance and $I_{\mathrm{int}}$ due to movement of ions across the membrane through different ion channels. In addition to leakage channels modeled by constant conductances, each modeled ion channel type is represented by a voltage- and time-dependent conductance $g_{\mathrm{ion}}(V,t)$ whose maximum value $\bar{g}_{\mathrm{ion}}$ is determined by the number of ion channels available at the membrane. Voltage- and time-dependence of ion channel conductances is determined by their dynamic opening and closing in response to changes in membrane potential, a phenomenon called gating. These models have proved successful to capture a variety of complex neuronal phenomena like excitability and its modulation, degeneracy, and homeostatic regulation (Marder et al., 2014).

Mathematically, the voltage current relationship of any conductance-based neuron model writes

$$\begin{aligned} I_C &= C\frac{\mathrm{d}V}{\mathrm{d}t} + g_{\mathrm{leak}}(V - E_{\mathrm{leak}}) = -I_{\mathrm{int}} + I_{\mathrm{ext}} \\ &= -\sum_{\mathrm{ion}\in\mathcal{I}} g_{\mathrm{ion}}(V,t)(V - E_{\mathrm{ion}}) + I_{\mathrm{ext}}, \end{aligned}$$

where $C$ is the membrane capacitance, $g_{\mathrm{ion}}$ is non-negative and gated between 0 (all channels closed) and $\bar{g}_{\mathrm{ion}}$ (all channels opened), $E_{\mathrm{ion}}$ and $E_{\mathrm{leak}}$ are the channel reversal potentials, $\mathcal{I}$ is the index set of intrinsic ionic currents, and $I_{\mathrm{ext}}$ is the current externally applied *in vitro* or the combination of synaptic currents.

In this paper, we focus our study of reliable neuromodulation on a stomatogastric (STG) neuron conductance-based model (Liu et al., 1998), but the proposed mechanisms are general. Thanks to the plethora of modulatory transmitters and neuropeptides flowing through the STG ganglion, STG neurons provide a prototypical testbed for neuromodulation studies (Marder et al., 2014). In the chosen STG neuron model, transitions between tonic spiking and bursting activities are of particular interest, as they relate to important behavioral switches in the STG ganglion (Meyrand et al., 1994).

### *3.2 Mapping ion channel expression to neuronal feedback gains*

The few feedback gains determining neuronal behavior are constructed from the voltage-dependent DIC (Drion et al.,

2015a). DICs are three voltage-dependent conductance curves $g_{\mathrm{f}}(V), g_{\mathrm{s}}(V), g_{\mathrm{u}}(V)$ that can be computed as linear functions of the maximal conductance vector $\bar{g}_{\mathrm{ion}}$ of the neuron model at each $V$

$$\begin{bmatrix} g_{\mathrm{f}}(V) \\ g_{\mathrm{s}}(V) \\ g_{\mathrm{u}}(V) \end{bmatrix} = f_{\mathrm{DIC}}(V) = S(V) \cdot \bar{g}_{\mathrm{ion}}\,, \tag{1}$$

where $S(V)$ is a sensitivity matrix that can be built using the methods in Drion et al. (2015a). Because of the specific feedback structure of conductance-based models, DICs shape neuronal spiking behavior and the three DICs differ in the timescale at which this shaping happens: fast $g_{\mathrm{f}}(V)$, slow $g_{\mathrm{s}}(V)$, and ultraslow $g_{\mathrm{u}}(V)$.

Values and signs of the DICs at specific voltages, mainly the threshold voltage $V_{\mathrm{th}}$, reliably determine the neuronal firing pattern (Drion et al., 2015a). For instance, a negative $g_{\mathrm{f}}(V_{\mathrm{th}})$, which corresponds to a local fast positive feedback, indicates that the neuron is able to fire a spike spontaneously around threshold voltage. A positive $g_{\mathrm{s}}(V_{\mathrm{th}})$, which corresponds to a slow negative feedback, indicates that, right after a spike, the neuron will tend to attenuate the excitation and bring back the neuron to rest voltage, while a negative $g_{\mathrm{s}}(V_{\mathrm{th}})$ indicates that the neuron will tend to fire other spikes to initiate a burst. In the case of bursting neuron, $g_{\mathrm{u}}(V_{\mathrm{th}})$ is always positive and is an indicator of the interburst frequency as well as the duty cycle, *i.e.*, ultraslow negative feedback.

### *3.3 The reference generator block: mapping target feedback gains to reference ion channel expression*

The reference generator block of the proposed adaptation mechanism transforms neuronal feedback gain reference trajectories into ion channel expression reference trajectories. That is, it transforms a functionally relevant reference signal, linked to the excitability type of the neuron, into a molecular reference signal that the feedback block can track.

The neuronal feedback gains are linked to ion channel maximal conductance through DICs. Target neuronal activity is defined as $g_{\mathrm{DIC}}(V_{\mathrm{th}}) = [f_{\mathrm{DIC}}(V_{\mathrm{th}})]_{t\in\mathcal{T}}$ with $\mathcal{T}$ being the set of timescales, *i.e.* $\mathcal{T} = \{f, s, u\}$ and $t$ being the modulated timescales (neuromodulator dependent). Given this target neuronal activity $g_{\mathrm{DIC}}(V_{\mathrm{th}}) \in \mathbb{R}^p$ for $p \leq 3$ neuronal feedback gains, and if there are $n$ modulated conductances, (1) defines a linear system of $p$ equations in $n$ unknowns. Because each modulator affects many conductances, in general $p \leq n$ and the system might be underdetermined, which leads to an infinite number of solutions (a whole subspace) in accordance with biological observation of ion channel degeneracy.

More formally, if the neuron expresses $N$ types of ion, of which $n$ are modulated and $m = N - n$ are unmodulated, the complete sensitivity matrix $S(V)$ used in the computation of the DICs at voltage $V$ and the complete maximum ion channel conductance vector $\bar{g}_{\mathrm{ion}}$ can be split in modulated ($S_{\mathrm{mod}}(V) \in \mathbb{R}^{p\times n}$, $\bar{g}_{\mathrm{mod}} \in \mathbb{R}^n$) and unmodulated ($S_{\mathrm{unmod}}(V) \in \mathbb{R}^{p\times m}$, $\bar{g}_{\mathrm{unmod}} \in \mathbb{R}^m$) components. Then the mapping from maximal conductances to DICs at threshold voltage can then be written as

$$g_{\mathrm{DIC}}(V_{\mathrm{th}}) = [S_{\mathrm{mod}}(V_{\mathrm{th}})\ S_{\mathrm{unmod}}(V_{\mathrm{th}})] \cdot \begin{bmatrix} \bar{g}_{\mathrm{mod}} \\ \bar{g}_{\mathrm{unmod}} \end{bmatrix}.$$

As only the threshold voltage is used, we drop voltage dependence of coefficient matrices and DICs in what follows. Isolating the unknowns modulated ion channel reference, the system becomes

$$S_{\mathrm{mod}} \cdot \bar{g}_{\mathrm{mod}} = g_{\mathrm{DIC}} - S_{\mathrm{unmod}} \cdot \bar{g}_{\mathrm{unmod}} =: g_{\mathrm{DIC_r}}\,. \tag{2}$$

Under the assumption that $n \geq p$ and $S_{\mathrm{mod}}$ has full row rank, the solution set to (2) is

$$\{\ \bar{g}_{\mathrm{mod}} \mid S_{\mathrm{mod}} \cdot \bar{g}_{\mathrm{mod}} = g_{\mathrm{DIC_r}}\ \} = \{\ \bar{g}_0 + z \mid z \in \mathcal{N}(S_{\mathrm{mod}})\ \}\,,$$

where $\bar{g}_0$ is any solution, *i.e.*, $S_{\mathrm{mod}} \cdot \bar{g}_0 = g_{\mathrm{DIC_r}}$ and $\mathcal{N}(S_{\mathrm{mod}})$ is the nullspace of $S_{\mathrm{mod}}$, *i.e.*,

$$\mathcal{N}(S_{\mathrm{mod}}) = \{z \in \mathbb{R}^n \mid S_{\mathrm{mod}} z = 0\}.$$

An important particular solution, that has the smallest norm as compared to any other solution, is

$$\bar{g}_0 = S_{\mathrm{mod}}^T (S_{\mathrm{mod}} S_{\mathrm{mod}}^T)^{-1} \cdot g_{\mathrm{DIC_r}} =: S_{\mathrm{mod}}^+ \cdot g_{\mathrm{DIC_r}}\,, \tag{3}$$

where $S_{\mathrm{mod}}^+$ is the Moore-Penrose generalized inverse of $S_{\mathrm{mod}}$ (Golub and Van Loan, 1996, Section 5.5.4). The matrix

$$S_{\mathrm{mod}}^+ S_{\mathrm{mod}} = P_{\mathcal{N}(S_{\mathrm{mod}})^\perp} \tag{4}$$

gives the projection onto the orthogonal complement of $\mathcal{N}(S_{\mathrm{mod}})$.

Equation 3 provides a reference values $\bar{g}_0$ for modulated ion channel expressions to the neuron to the desired excitability type. Biologically a molecular regulatory network can implement this equation. Note that the feedforward block depends and therefore must access the overall conductance state $\bar{g}_{\mathrm{ion}}$ of the neuron. This means that the feedforward block adapts to any change in the expression of unmodulated ion channels. Because a neuron cannot measure its own ion channel expression levels, the dependence of the proposed adaptation mechanism in $\bar{g}_{\mathrm{ion}}$ is not biologically plausible. We will address this issue in future works, by using signals measurable by the neuron such as $V$ or $[\mathrm{Ca}^{2+}]$ and adding a homeostatic control loop inspired by O'Leary et al. (2014) whose output provides a biological version of $\bar{g}_{\mathrm{ion}}$. Putting together homeostasis and molecular regulatory network is an idea already explored in Franci et al. (2020) to make the homeostatic controller in O'Leary et al. (2014) robust to unmatched disturbances.

### *3.4 The feedback block: ion channel expression regulation and membrane turnover*

The feedback block takes the form of a classical PI control system with gains $K_{\mathrm{p}}$ and $K_{\mathrm{i}}$ controlling a plant describing the molecular dynamics of each modulated ion channel. The input of the PI controller is an error signal vector $e \in \mathbb{R}^n$. The dynamics describing ion channel creation and transport are modeled as a linear two compartments (the intracellular and membrane ones, with state variables $i \in \mathbb{R}^n$ and $\bar{g}_{\mathrm{mod}} \in \mathbb{R}^n$, respectively) model communicating at rate $\alpha$ and with continuous degradation of intracellular ion channels at rate $\beta$, biologically motivated by the membrane turnover. The control input ($u \in \mathbb{R}^n$) consists in a controlled translation mechanism that synthesizes intracellular ion channels ready to integrate the membrane through diffusion and to participate in excitability shaping of the neuron.

The dynamics of the feedback block for $n$ neuromodulated ion channel writes

$$\dot{\bar{i}}_j = \alpha \cdot \bar{g}_j - (\alpha + \beta) \cdot \bar{i}_j + u_j$$
$$\dot{\bar{g}}_j = \alpha \cdot \bar{i}_j - \alpha \cdot \bar{g}_j, \quad j = 1, \ldots, n.$$

The control $u_j$ is generated by a PI controller

$$u_j(t) = K_\mathrm{p} \cdot e_j(t) + K_\mathrm{i} \cdot \int_0^t e_j(\tau)\, d\tau. \tag{5}$$

To ensure that the steady-state value imposed by the PI controller for the modulated ion channels will make the neuronal feedback gains match the target ones, the error vector $e$ in (5) is defined as

$$e = r - y := \bar{g}_0 - P_{\mathcal{N}(S_\mathrm{mod})^\perp} \cdot \bar{g}_\mathrm{mod}\,,$$

where $r = \bar{g}_0$ is the reference of the feedback block and $y = P_{\mathcal{N}(S_\mathrm{mod})^\perp} \bar{g}_\mathrm{mod}$ is its output. Thanks to PI action, the overall system will reach steady state when the error vector is identically zero, *i.e.*, when $e = 0_n$. By developing $e$ using (3) and (4), one has

$$e = S^+_\mathrm{mod} \cdot g_{\mathrm{DIC_r}} - S^+_\mathrm{mod} S_\mathrm{mod} \cdot \bar{g}_\mathrm{mod}.$$

Imposing $e = 0_n$ leads

$$S^+_\mathrm{mod} S_\mathrm{mod} \cdot \bar{g}^*_\mathrm{mod} = S^+_\mathrm{mod} \cdot g_{\mathrm{DIC_r}}\,,$$

where $\bar{g}^*_\mathrm{mod}$ denote the modulated conductance values at steady state. Multiplying both sides of the last equality from the left by $S_\mathrm{mod}$ gives

$$\underbrace{S_\mathrm{mod} S^+_\mathrm{mod}}_{I_p} S_\mathrm{mod} \cdot \bar{g}^*_\mathrm{mod} = \underbrace{S_\mathrm{mod} S^+_\mathrm{mod}}_{I_p} \cdot g_{\mathrm{DIC_r}}$$

and therefore

$$S_\mathrm{mod} \cdot \bar{g}^*_\mathrm{mod} = g_{\mathrm{DIC_r}}, \tag{6}$$

which means that, at steady state, the overall system will converge towards values of neuromodulated ion channels that match the actual model DICs with the target ones, even if the system (2) is underdetermined. Therefore, the adaptive neuromodulation-controlled system ensure that, with $n$ ($\geq p$) appropriate neuromodulated ion channels ($S_\mathrm{mod}$ full row rank), the excitability of the neuron can be shaped by fixing neuronal feedback gains. The adaptation mechanism, and especially the feedback block, is ensured to be stable as long as the PI feedback is slow enough. Under-determinacy of (2) implies that the steady-state solution enforced by the PI controller is not unique, which provides a new mechanistic explanation for neuronal degeneracy.

## 4. RELIABLE NEUROMODULATION FROM ADAPTIVE GAIN CONTROL

The robustness of the proposed adaptive gain control scheme was tested in simulation on neurons having highly variable sets of maximal conductances, in agreement with biological data. We focus our simulation on neuromodulation-dependent spiking to bursting transitions, with slow calcium and A type potassium channels ($\bar{g}_\mathrm{CaS}$ and $\bar{g}_\mathrm{A}$, respectively) as targets of neuromodulators. Spiking to bursting transitions are controlled by specific values of $g_\mathrm{s}(V_\mathrm{th})$ and $g_\mathrm{u}(V_\mathrm{th})$ (Drion et al., 2015a). $g_\mathrm{f}(V_\mathrm{th})$ is chosen to not be controlled, as it correlates with spike upstroke but does not affect spiking to bursting transitions. Therefore, the problem results in a two dimensional linear system where the unknowns are the ion channel

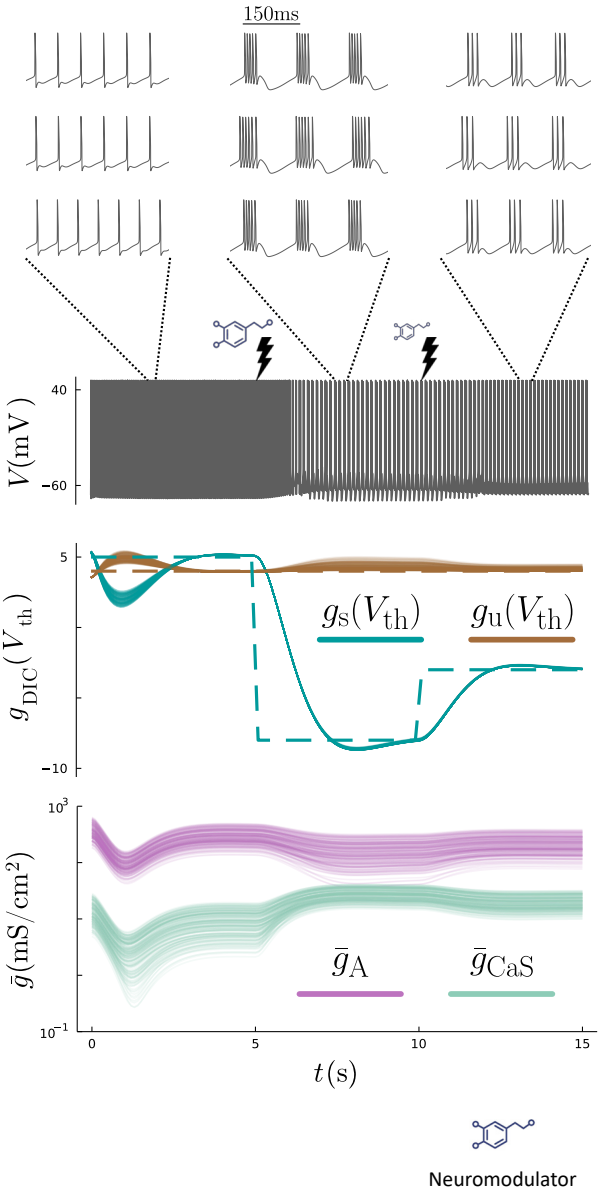


Fig. 3. Virtual experiment of the adjustment mechanism applied to 200 STG models with heterogeneous nominal parameters. In this experiment, three different states are targeted during the three different thirds of the simulation, respectively tonic spiking, strong bursting and light bursting (triplets). A typical $V$ trace for each third of the simulation is shown on top for three randomly chosen model neurons with different parameter values, which proves the robustness of the modulation mechanism to heterogeneity. We simulated a bath application with a strong increase in the neuromodulator concentration at $t = 5\,\mathrm{s}$ and a slight decrease at $t = 10\,\mathrm{s}$. This modulation is achieved by maintaining $g_\mathrm{u}(V_\mathrm{th})$ constant and by regulating $g_\mathrm{s}(V_\mathrm{th})$ through the proposed neuromodulation control scheme. Target values of DICs are depicted in dashed lines while actual values of neuronal feedback gains are depicted in full lines. The target $g_\mathrm{s}(V_\mathrm{th})$ is achieved by modulating only two slow ion channel conductances, namely $\bar{g}_\mathrm{A}$ and $\bar{g}_\mathrm{CaS}$, bottom.

expression reference trajectories, and solutions of (6) are uniquely determined.

These simulations reproduce a bath application that is constructed as follows (Fig. 3): first, no neuromodulator is applied to the neurons, which is emulated by setting the value of $g_{\mathrm{s}}(V_{\mathrm{th}})$ to a positive value. In that state, the target activity is single spike firing. After 5 seconds, $g_{\mathrm{s}}(V_{\mathrm{th}})$ is set to a strongly negative value, emulating the application of a strong concentration of a bursting-inducing neuromodulator, such as proctoline or pilocarpine. $g_{\mathrm{s}}(V_{\mathrm{th}})$ is then reduces to a less negative value at 10 seconds to model a decrease in neuromodulator concentration. The target value for $g_{\mathrm{u}}(V_{\mathrm{th}})$ is kept constant during the whole simulation, as we consider that the neuromodulator only tunes the slow conductance value. It is important to note that $g_{\mathrm{s}}(V_{\mathrm{th}})$ is the only externally modified input to the model in this virtual experiment, every other inputs and parameters, including channel maximal conductances being autonomously tuned by the adaptive control mechanism.

Figure 3 shows simulation results for 200 highly variable parameter sets of maximal conductance values. In all these models, the adaptive control system is capable of reliably reaching the three target firing activities corresponding to the three neuromodulation levels by tuning the maximal conductance values $\bar{g}_{\mathrm{CaS}}$ and $\bar{g}_{\mathrm{A}}$ in a neuron-dependent manner. This shows that such simple yet carefully designed adaptive controller targeting two scalar reference gain values is capable of reliably controlling the behavior of a complex neuron model. The same experiment showed similar results on a dopaminergic neuron model, which illustrates the generality of the proposed approach.

## 5. CONCLUSIONS

In this work, we designed an adaptive control mechanism that achieves reliable neuromodulation in highly heterogeneous neurons. The control mechanism is motivated by the specific structure of molecular signaling triggered by neuromodulators, which involves second messenger and intracellular signaling cascades in molecular regulatory networks to link changes in neuromodulator concentration to changes in ion channel maximal conductances. We showed that despite the high complexity and dimensionality of neuronal dynamics, reliable neuromodulation could be achieved by tuning the values of a few neuron feedback gains acting on different timescales and localized around threshold potential. A feedforward mechanism transforms these target gains into neuron-dependent targets for the maximal conductance of a subset of neuromodulated ion channels. Future work will aim at coupling the proposed control scheme with previously published homeostatic neuronal control schemes and at the implementation of the resulting controller in neuromorphic hardware.

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## Appendix A. PARAMETER VALUES

Table A.1. Parameter values

| Parameter | Value | Units |
|---|---|---|
| $\alpha$ | $5 \cdot 10^{-3}$ | $\mathrm{ms}^{-1}$ |
| $\beta$ | $5 \cdot 10^{-3}$ | $\mathrm{ms}^{-1}$ |
| $K_{\mathrm{p}}$ | $3 \cdot 10^{-4}$ | $\mathrm{ms}^{-1}$ |
| $K_{\mathrm{i}}$ | $5 \cdot 10^{-6}$ | $\mathrm{ms}^{-1}$ |