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Linking dynamics of the inhibitory network to the input structure

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Abstract

Networks of inhibitory interneurons are found in many distinct classes of biological systems. Inhibitory interneurons govern the dynamics of principal cells and are likely to be critically involved in the coding of information. In this theoretical study, we describe the dynamics of a generic inhibitory network in terms of low-dimensional, simplified rate models. We study the relationship between the structure of external input applied to the network and the patterns of activity arising in response to that stimulation. We found that even a minimal inhibitory network can generate a great diversity of spatio-temporal patterning including complex bursting regimes with non-trivial ratios of burst firing. Despite the complexity of these dynamics, the network's response patterns can be predicted from the rankings of the magnitudes of external inputs to the inhibitory neurons. This type of invariant dynamics is robust to noise and stable in densely connected networks with strong inhibitory coupling. Our study predicts that the response dynamics generated by an inhibitory network may provide critical insights about the temporal structure of the sensory input it receives.

Keywords

Inhibitory neurons; Information coding; Neural network; Olfactory system; Spike sequences; Odor discrimination

1 Introduction

Neuronal networks possess mechanisms that can organize groups of synchronously spiking neurons into elaborate temporal sequences (Hebb 1949). These spatiotemporal patterns form the basis of perception (Gray and Singer 1989), memory (Cheng and Frank 2008) and action (Bouyer et al. 1987). Recordings from hippocampal networks (Bonifazi et al. 2009), mitral cells in the olfactory bulb (Schoppa 2006), cortical pyramidal neurons, and central pattern generators in vertebrates (Grillner 2003) and invertebrates (Marder and Calabrese 1996)

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have shown that the spatiotemporal patterning in neuronal networks, to a large extent, depends on the temporal and the spatial distribution of inhibition. A single inhibitory neuron (or group of synchronously firing inhibitory neurons) can shape the timing of the firing in many excitatory cells, therefore, creating assemblies of synchronously spiking principal neurons (Bazhenov and Stopfer 2010; Assisi et al. 2011). The dynamics of such assemblies may then be responsible for encoding sensory information (Laurent 2002).

A well-known example of a biological system where inhibition plays a critical role in establishing temporal sequences of spiking in the excitatory neurons is the insect antennal lobe – the first relay of the insect olfactory system (Laurent and Davidowitz 1994). Odors are represented in the antennal lobe as sequences of transiently synchronous principal neurons that are entrained by the activity of groups of inhibitory interneurons (MacLeod et al. 1998; Bazhenov et al. 2001). Similar activity patterns are also found in the mitral cells in the mouse and zebrafish olfactory bulb (Friedrich and Stopfer 2001; Friedrich and Laurent 2004; Schoppa 2006; Jones et al. 2007). It is hypothesized that the structure of synchronously spiking ensembles of neurons and the order of their activation depends strongly on the network connectivity and external stimulation and contribute to the encoding of olfactory information (Laurent et al. 1996). In hippocampal (Foster and Ma 2006) and cortical networks, sequences of neuronal activation during sleep are believed to underlie the replay of awake experiences – a process critical for memory consolidation. Precise patterns of activity of the excitatory cells, which recur over durations of hours, often arise in the cortical networks and depend on synaptic inhibition (Beggs and Plenz 2003; Beggs 2004).

Inhibition is ubiquitous in neural circuits and is often manifested in two motifs, feedforward and feedback (Bazhenov and Stopfer 2010). These motifs have different characteristics that may be further shaped by the plastic, time-dependent, dynamic properties of the circuit. In different brain systems including olfactory (Leitch and Laurent 1993), thalamic (Ulrich and Huguenard 1997) and cortical (Kawaguchi and Kubota 1993; 1997; 1998) networks, inhibitory interneurons are extensively mutually interconnected by GABAergic synapses, thus creating inhibitory sub-networks with complex dynamics.

In this new study, we investigated the relationship between the inputs and connectivity of inhibitory neuron networks and the activity patterns produced by the network. In contrast to previous studies, we focused on strongly heterogeneous and asymmetric inhibitory networks where external inputs differ significantly across the neurons. We generalized the theoretical method of the low-dimensional description of neuronal dynamics (Benda and Herz 2003) and applied it to networks of pulse-coupled inhibitory neurons. We show that the heterogeneity of the input profile leads to rich spatiotemporal bursting dynamics, including non-regular patterns and complex bursting regimes, when neurons are locked in a non-trivial activation ratio (2:3, 1:2, 1:3 etc). These effects, caused by strong heterogeneity of the input profile, have not been sufficiently studied in the past. Despite the overall complexity of the bursting patterns, we found that the inhibitory networks with dense and strong connections may show simple features, which clearly reflects the network stimulation profile. While this study is inspired by odor processing in the insect olfactory system, our results are generic and can be applied to different neuronal systems where networks of inhibitory neurons are involved in information processing.

2 Methods

2.1 Basic mathematical model: leaky adaptive integrate-and-fire neuron

In this study we used a model of spiking neurons displaying two generic dynamical properties commonly found across different classes of the biological neurons: (i) being stimulated by a constant external current, it produces periodic spiking activity; (ii) it shows spike-frequency adaptation. One of the most simple mathematical models reproducing qualitatively such behavior is an adaptive leaky integrate-and-fire model (Treves 1993):

$$\begin{aligned} C_m \frac{dV_i}{dt} &= g_0(V_0 - V_i) + I_i \\ I_i &= g_i^K (V_K - V_i) + \sum_{j=1}^N G_{ij} s_j (V_s - V_i) + I_i^{ext} + \eta \xi_i \\ \frac{dg_i^K}{dt} &= -\frac{g_i^K}{\tau_g} + \Delta g \sum_n \delta(t - t_n) \\ \frac{ds_i}{dt} &= -\frac{s_i}{\tau_s} + \Delta s \sum_n \delta(t - t_n) \end{aligned} \quad (1)$$

System (1) describes dynamics of the neural network, which consists of N neurons, index i refers to the i -th element of the network ($i = 1, \dots, N$). $V_i(t)$ is a membrane potential of the i -th neuron, the variable g_i^K stands for the active potassium-type conductance and $s_i(t)$ corresponds to an active conductance of the synapses directed from the i -th neuron to the other neurons in the networks. The parameter V_0 denotes reversal potential of the leak current, g_0 – passive conductance and C_m is membrane capacitance.

In this model, when the membrane potential $V_i(t)$ reaches the threshold value V_{thr} the model generates a spike. After that the membrane potential resets: $V_i \rightarrow V_{ahp}$. The membrane current

$$I_i = I_a + I_i^{syn} + I_i^{ext} + \eta \xi_i$$

consists of four parts: (i) the adaptation current $I_a = g_i^K (V^K - V)$ is responsible for spike-frequency adaptation, (ii) the current $I_i^{syn} = \sum_j G_{ij} s_j (V_s - V_i)$ describes synaptic input from the network where coefficients G_{ij} form a constant coupling matrix. Note, that the sum goes over all presynaptic neurons j and integrates weighted active synaptic conductances $G_{ij} s_j$ (directed from neuron j to i). (iii) The term I_i^{ext} denotes constant external current (stimulus), and (iv) the term $\eta \xi_i(t)$ corresponds to the fluctuations in the afferent input which are given by a white noise process with the following properties: $\langle \xi_i(t) \rangle = 0$, $\langle \xi_i(t) \xi_i(t - t_0) \rangle = \delta(t - t_0)$. Here $\delta(t)$ stands for Dirac delta function, constant η determines the strength of the noise.

Whenever the neuron produces a spike, the variable g_i^K is shifted by the value

$\Delta g: g_i^K \rightarrow g_i^K + \Delta g$, so the absolute value of the adaptation current I_a increases, which produces decrease of the firing frequency (reversal potential is negative $V_K = -85$ mV).

Mathematically, it is described by the sum $\Delta g \sum_n \delta(t - t_n)$ in the third equation of the system (1) where t_n denote spike times. Between spikes (when $t \neq t_n$) the variable g_i^K decays exponentially with characteristic time scale τ_g . Variables $s_i(t)$ and V_s correspond to the

active conductance and reversal potential of the synapses correspondingly. The dynamics of the synaptic conductance s_j is similar to the dynamics of the variable g_i^K . The coefficients G_{ij} in the equation for the synaptic current (see the second equation of system (1)) describe weights of synaptic connection from the j -th to the i -th neuron. In our studies we always assume $G_{ii} = 0$, so there are no any self-inhibiting connections in the network. Following the original paper (Treves 1993), we use the following set of parameters throughout the paper (unless specified): $C_m = 0.375$ nF, $g_0 = 25$ nS, $V_0 = -73$ mV, $V_{thr} = -53$ mV, $V_{ahp} = -63$ mV, $V_K = -85$ mV, $V_s = -70$ mV. We assume purely deterministic case (no noise) $\eta = 0$ except the section “Stability against perturbations” and “Generalization for larger networks $N > 3$ ”.

As we will show further, the system (1) represents “minimal” dynamical model with the relatively simple mathematical structure. Nevertheless, the model contains all the necessary dynamical features for non-trivial pattern formation.

2.2 Hodgkin-Huxley-type model

We also used a realistic conductance-based model with similar dynamical properties to the system (1). Namely, we adapted the equations described in (Traub 1982; Kilpatrick and Ermentrout 2011). The model contains classical sodium and potassium currents for the fast spike-generating mechanism, calcium dynamics and slow calcium-dependent potassium current responsible for spike-frequency adaptation. The membrane potential for each neuron is governed by the following equation:

$$C_m \frac{dV_i}{dt} = I_{ion}(V_i) + I_i^{syn} + I_i^{ext}. \quad (2)$$

The ionic current $I_{ion}(V_i)$ governing intrinsic (isolated, without any external synaptic inputs) dynamics reads:

$$I_{ion}(V_i) = g_{Na} m_i^3 h_i (V_{Na} - V_i) + g_K n_i^4 (V_K - V_i) + g_L (V_L - V_i) + G_{Ca}(V_i)(V_{Ca} - V_i) + g_{ahp} \frac{c_i}{c_i + k_d} (V_K - V_i) \quad (3)$$

where $G_{Ca}(V) = g_{Ca} / (1 + \exp(-(V - V_{th})/V_{shp}))$. The gating variables m_i , h_i , n_i evolve according to:

$$\frac{dx_i}{dt} = \alpha_x(V_i)(1 - x_i) - \beta_x(V_i)x_i,$$

where x_i is one of gating variables. The functions $\alpha_x(V)$ and $\beta_x(V)$ are:

$$\begin{aligned}\alpha_m(V) &= \frac{0.32(54+V)}{1-\exp(-0.25(V+54))}, \\ \beta_m(V) &= \frac{0.28(V+27)}{\exp(0.2(V+27))-1}, \\ \alpha_h(V) &= 0.128(-(50+V)/18), \\ \beta_h &= \frac{4}{1+\exp(-0.2(V+27))}, \\ \alpha_n(V) &= \frac{0.032(V+52)}{1-\exp(-0.2(V+52))}, \\ \beta_n(V) &= 0.5\exp(-(57+V)/40).\end{aligned}$$

Calcium concentration c_i obeys the following equation:

$$\frac{dc_i}{dt} = -\alpha_{Ca} G_{Ca}(V_i)(V_i - V_{Ca}) - \frac{c_i}{\tau_{Ca}}$$

and governs calcium-dependent hyperpolarizing potassium current

$$I_{AHP} = g_{ahp} \frac{c_i}{c_i + k_d} (V_K - V_i), \text{ which is responsible for spike-frequency adaptation.}$$

The synaptic input was modeled according to $I_i^{syn} = \sum_j G_{ij} s_j (V_{syn} - V_j)$ where synaptic variables s_j are governing by the following equation:

$$\frac{ds_i}{dt} = \alpha_s S(V_i)(1 - s_i) - \beta_s V_i$$

where

$$S(V) = \frac{1}{1 + \exp(-100(V - 20))}.$$

Below we list all the parameters that were fixed in the simulations (unless specified in the description of calculations):

$$\begin{aligned}V_K &= -100 \text{ mV}, V_{Na} = 50 \text{ mV}, V_L = -67 \text{ mV}, V_{Ca} = 120 \text{ mV}, V_{shp} = 2.5 \text{ mV}, V_{syn} = \\ &-80 \text{ mV}, V_{th} = 25 \text{ mV}, g_L = 0.2 \text{ mS/cm}^2, g_K = 80 \text{ mS/cm}^2, g_{Na} = 100 \text{ mS/cm}^2, g_{Ca} = \\ &1 \text{ mS/cm}^2, C_m = 1 \text{ } \mu\text{F/cm}^2, \tau_{Ca} = 1000 \text{ ms}^{-1}, \alpha_{Ca} = 0.001, \alpha_s = 5 \text{ ms}^{-1}, \beta_s = 0.5 \\ &\text{ms}^{-1}.\end{aligned}$$

2.3 The method of reduction to phenomenological low-dimensional model: an overview

Below we describe the method of reduction (Benda and Herz 2003) of the oscillatory model (1) to even simpler averaged model. The aim of this procedure is to reduce the relatively complex spiking models to the simpler low-dimensional system for analytical description of the observed patterns and dynamics. In (Benda and Herz 2003) it was shown that under several assumptions any spiking model that contains (i) fast subsystem for spikes generation and (ii) slow adaption current responsible for the spike-frequency adaptation, can be effectively described by the special class of reduced low-dimensional models. In this approach we separate fast spike-generating subsystem and slow subsystem, which is

responsible for the spike-frequency adaptation. As a result we approximate the adaptation gating variable $g^K(t)$ (we skip the index i here because we describe the method for a single neuron) by its running average $A(t)$ calculated over the interspike intervals $T_{isi}(t)$:

$$g^K(t) \approx A(t) = T_{isi}^{-1}(t) \int_{t-T_{isi}(t)/2}^{t+T_{isi}(t)/2} g^K(t') dt', \quad (4)$$

here $T_{isi}(t)$ denotes the time-dependent interspike intervals (time dependence arise due to the spike-frequency adaptation). Thus, in this approach we skip the details of fast dynamics of the transmembrane potential $V(t)$ and replace all the dependences on $V(t)$ by functions of the firing frequency f . The general form of the model reads:

$$\begin{aligned} \tau[1+\varepsilon(f)] \frac{dA}{dt} &= A_\infty(f) - A, \\ f &= F_0(I^{ext} - \sigma A[1+\gamma(f)]). \end{aligned} \quad (5)$$

Here the variable $A(t)$ (4) describes the averaged dynamics of gating variable $g^K(t)$ (in other words, $A(t)$ is a mean value of conductance of the slow adaptive current) and $f(t)$ (second equation in (5)) stands for instantaneous firing frequency of the neuron. The function $A_\infty(f)$ is a limiting value of the adaptation variable $A(t)$ for a given firing frequency f : $A(t) \rightarrow A_\infty(f_0)$ as $t \rightarrow \infty$ if firing frequency $f = f_0$. The function $F_0(I^{ext})$ describes dependence of the firing frequency f on the constant input current I^{ext} in the case of absence of adaptation current I_a (the synaptic current is absent since we considering only one neuron). In other words, the function $F_0(I)$ represents $f-I$ relation of the spike-generating mechanism and does not depend on the adaptation. The characteristic time scale of dynamics of the variable $A(t)$ is determined by the parameter τ (see the first equation in (5)) and may also depend on f through additional factor $1 + \varepsilon(f)$ ($\varepsilon(f)$ is usually negligible).

One of the fundamentals of the reduction method is an assumption that averaged effect of the adaptation current I_a is equivalent to a shift of the input current I^{ext} to the lower values what produces decrease (adaptation) of the firing frequency f (since $F_0(I^{ext})$ is a monotonically increasing function of f). Therefore in the Eq. (5) the effect of the frequency adaptation is represented by the term $I^{ext} - \sigma A[1 + \gamma(f)]$ where the function $\gamma(f)$ represents possible dependence of the adaptation effect on f and it is usually negligible ($\gamma(f) \ll 1$). The parameter σ is a constant to be determined further. Thus, we assume that the effect of the adaptation current I_a on the firing frequency f in the second equation of (5) is proportional to the averaged adaptation state $A(t)$ and its dependence on f is negligible. The latter assumption is valid if two conditions are satisfied in the initial spiking model:

- First, the dynamics of the adaptation variable (variable g^K in the case of the integrate-and-fire model (1)) should be sufficiently slow compare to the spiking frequency. It can be only in the case when the frequency f is high enough and parameter τ_g is large.
- Second, the coupling of the adaptation current to the spike generating mechanism should be weak enough. The weak coupling assumption implies that

the fast fluctuations of I_a do not produce any significant effect on the firing frequency f and time course of the voltage $V(t)$. Further we will show that this assumption is always valid in our case.

Thus, the process of reduction of the model (1) to the low-dimensional system (4) requires the determination of the parameters τ , σ function $A(f)$ and the validation of the assumptions $\varepsilon(f) \ll 1$, $\gamma(f) \ll 1$.

2.4 Reduction of integrate-and-fire model to averaged low-dimensional system: a single neuron case

Following (Benda and Herz 2003) we used the simplest way to define unknown quantities A_∞ and τ . The definition is based on the analysis of the dynamical equation for the adaptation variable $g^K(t)$ (the third equation in (1)) in response to the periodic train of spikes with constant period $T = 1/f$:

$$\frac{dg^K}{dt} = -\frac{g^K}{\tau_g} + \Delta g \sum_n \delta(t - t_n) \quad (6)$$

In contrast to the entire system (1), here we assume that $t_n = n/f$ where f is a *constant* frequency of delta peaks (at $t = t_n$). The dynamics of the averaged adaptation state $A = \langle g^K \rangle_T$ (averaged over the period T) can be perfectly described by an exponential relaxation process given by the first equation in the system (5) with appropriately adjusted time scale τ and function $A_\infty(f)$. Indeed, Eq. (6) can be easily transferred to the linear map

$$g_{n+1} = g_n e^{-T/\tau_g} + \Delta g, \quad (7)$$

where g_n denotes values of $g^K(t)$ at discrete moments of time $t = t_n$. The stable fixed point for g_n is $g^* = \Delta g / (1 - e^{-T/\tau_g})$, hence, the stationary averaged adaptation state $A_\infty(f)$ has the following form:

$$A_\infty(f) = T^{-1} \int_0^T g^* e^{-t/\tau_g} dt = c_a(\Delta g, \tau_g) \cdot f,$$

where $c_a(\Delta g, \tau_g) = \Delta g \tau_g$. In the limit $T/\tau_g \ll 1$ the time course of the averaged adaptation state $A(t)$ can be approximated by dynamics of the variable g_n (Eq. (7)), which decays exponentially to its stationary value g^* with characteristic time scale τ_g (in continuous time t). Therefore, for sufficiently small T/τ_g we may assume that characteristic time scale of the variable $A(t)$ (parameter τ) is equal to parameter τ_g and function $\varepsilon(f)$ is negligible ($\varepsilon(f) \ll 1$). Figure 1a supports our assumption showing examples of the function $\varepsilon(f)$ calculated for typical range of the parameters τ_g and Δg , which we used in our study.

As a next step, we check assumption that the averaged effect of the adaptation current I_a is equivalent to the shift of the input current I^{ext} and that this shift is linearly proportional to $A(t)$. Here we would like to stress that further in this section we use direct simulation of the

Eq. (1) (not just one Eq. (6)) and the term f below denotes instantaneous firing frequency of the neuron. When the external I^{ext} current was applied, the neuron generated spikes with a certain frequency. Spiking activity led to accumulation of the adaptation variable $g^K(t)$ in the model (1) (or accumulation of calcium in the conductance-based model (2)), which led to increase of the adaptive current in both models. As a result, the firing frequency f of the neuron decreased (inter-spike intervals T_{isi} increased) as time grew (an example is given in Fig. 1c). The changes of the interspike intervals $T_{isi}(t)$ in time can be associated with a certain input current $\tilde{I}$: $T_{isi} = 1/F_0(I^{ext} - \tilde{I})$. Here the function $F_0(I)$ represents $f-I$ relation of the neuron without adaptation (when $I_a = 0$). The value of $\tilde{I}$ is supposed to be *constant* during each interspike interval T_{isi} . To calculate $F_0(I)$, we assumed that $I = \text{const}$ in the first equation of the system (1) and determined the time T of excursion of the membrane potential $V(t)$ from V_{ahp} to V_{thr} :

$$F_0(I) = T^{-1} = \frac{g_0}{C_m} \left[\ln \left(\frac{g_0(V_{ahp} - V_0) - I}{g_0(V_{thr} - V_0) - I} \right) \right]^{-1}$$

Using $f-I$ relation, the current $\tilde{I}$ can be determined as

$$\tilde{I} = F_0^{-1}(1/T_{isi}) - I^{ext} = g_0 \frac{V_{thr} - V_0 + (V_0 - V_{ahp})e^{-g_0 T_{isi}/C}}{1 - e^{-g_0 T_{isi}/C}} - I^{ext} \quad (8)$$

The core idea behind the reduction method is an assumption that the current $\tilde{I}$ is linearly proportional to the averaged (on T_{isi}) value of the adaptation variable g^K : $\tilde{I} = \sigma \langle g^K(t) \rangle_{T_{isi}}$ (σ is constant).

Using direct solution of the system (1) for a single neuron ($N = 1$), we calculated the time course of the variables $V(t)$, $g^K(t)$ and identified interspike intervals T_{isi} and values of the averaged adaptation state $\langle g^K(t) \rangle_{T_{isi}}$ (the system started from the resting state and stimulation current I^{ext} was sufficient to induce spiking). Next, we compared the current $\tilde{I}$ (calculated according to (8)) with the averaged value of the adaptation variable $\langle g^K \rangle_{T_{isi}}$ to check the hypothesis of linear relation $\tilde{I} = \sigma \langle g^K \rangle_{T_{isi}}$. Hence, σ was defined as a parameter, which provides the best linear approximation for the function $\tilde{I}(\langle g^K \rangle_{T_{isi}})$ which was obtained from direct solution of (1). Function $\gamma(f)$

$$\gamma(f) = \tilde{I} / (\sigma \langle g^K \rangle_{T_{isi}}) - 1 \quad (9)$$

represents an error of the linear approximation and it is relatively small for a typical range of parameters that we used in our study (Fig. 1b). Therefore we concluded that the effect of the adaptation current on the firing frequency of the neurons can be described by a constant shift of external current as $I^{ext} \rightarrow I^{ext} - \sigma A$ (recall that $A = \langle g^K \rangle_{T_{isi}}$) where parameter σ is a

slope of $\tilde{I}(\langle g^K \rangle_{T_{isi}})$ linear approximation, and the error function $\gamma(f)$ can be skipped from consideration.

In summary, the reduced model (4) in the case of integrate-and-fire neuron reads:

$$\begin{aligned}\tau \frac{dA}{dt} &= A_\infty(f) - A, \\ A_\infty(f) &= c_a(\tau_g, \Delta g) \cdot f, \\ f &= F_0(I^{ext} - \sigma A).\end{aligned}\quad (10)$$

where $c_a(\tau_g, g) = \tau_g \cdot g$ and σ are constant parameters which can be approximated from dynamics of the system (1) for a single neuron $N=1$. Parameter c_a depends only on the details of the adaptation mechanism (quantities τ_g and g), while the value of σ depends also on the parameters of the spike generating mechanism. It is worth noting that in the limiting case of a slow adaptation ($T/\tau_g \ll 1$) and weak coupling of the adaptation mechanism to spike-generation, parameter σ can be computed analytically (Benda and Herz 2003). However, in our study we prefer to use direct definition from numerical solution of the system (1) to obtain a better accuracy of the low-dimensional approximation.

Here we emphasize, that both conditions for the reduction procedure (Benda and Herz 2003) are valid throughout all our simulations: (i) the time scale of adaptation τ_g is low in comparison to the firing frequency f , such that $T_{isi}/\tau_g \ll 1$, which provides $\varepsilon(f) \ll 1$; (ii) the condition of the weak coupling mechanism is fulfilled, which was confirmed by direct calculation of the function $\gamma(f) \ll 1$. As a result the low-dimensional system efficiently predicts firing frequency and adaptation state of the oscillatory model (Fig. 1c,d), which was confirmed by calculation of the relative error of the low-dimensional approximation (Fig. 1e).

2.5 Extension of the reduction method to network dynamics

In order to use phenomenological low-dimensional model (10) for a network of coupled neurons, we need to consider the model (1) in the limit of the infinitely strong and fast synaptic coupling. In the latter case the system (1) represents pulse-coupled network: generation of spike in the presynaptic neuron produces rapid decrease of potential $V_{post} \rightarrow V_{syn}$ in the postsynaptic neuron. First, let us consider the simplest situation when the adaptation currents are absent $I_a = 0$ in all neurons. Now, we assume that presynaptic neuron generates periodic train of spikes with certain frequency f^{pre} without adaptation. Then, depending on the frequency f^{pre} , the dynamics of the postsynaptic neuron can be of two types: (i) if frequency f^{pre} is above certain critical value $f^{pre} > f^{cr}$, the postsynaptic neuron is completely suppressed by presynaptic inhibition, (ii) in opposite, if $f^{pre} < f^{cr}$, the rate of inhibition is not enough for suppression and the post-synaptic neuron generates spikes with certain frequency $f^{post} > 0$. The critical frequency f^{cr} can be easily defined in the pulse-coupled limit: $f^{cr} = T_s^{-1}$ where T_s is a time of excursion of the postsynaptic potential from V_s to V_{thr} :

$$f^{cr} = T_s^{-1} = \frac{g_0}{C_m} \left[\ln \left(\frac{g_0(V_s - V_0) - I_{post}^{ext}}{g_0(V_{thr} - V_0) - I_{post}^{ext}} \right) \right]^{-1}$$

Thus, f^{cr} depends on the parameters of the spike-generating mechanism and on the input current I_{post}^{ext} in the postsynaptic neuron.

If we now take the adaptation into account, then, the critical frequency f^{cr} depends on the state and dynamics of the adaptive variable g_{post}^K in the postsynaptic neuron. However, when conditions of reduction to the low-dimensional system (10) are satisfied (see above), the effect of the adaptation current I_a in the postsynaptic neuron is simply equivalent to the shift of the input current I_{post}^{ext} to $I_{post}^{ext} - \tilde{\sigma} A_{post}(t)$. This allows defining the critical frequency f^{cr} in terms of the low-dimensional averaged model:

$$f^{cr} = T_s^{-1} = \frac{g_0}{C_m} \left[\ln \left(\frac{g_0(V_s - V_0) - I_{post}^{ext} + \tilde{\sigma} A_{post}(t)}{g_0(V_{thr} - V_0) - I_{post}^{ext} + \tilde{\sigma} A_{post}(t)} \right) \right]^{-1}.$$

where $\tilde{\sigma}$ is determined in the same way as σ , the only difference is that now one should assume that postsynaptic neuron is always shifted to the value V_s due to the inhibition and not to V_{ahp} . The variable $A_{post}(t)$ denotes averaged values of the adaptation variable $g^K(t)$ (see Eq. (4)) in the postsynaptic neuron.

Taking all this into account, we can define the low-dimensional phenomenological system for a network of globally pulse-coupled oscillators (Eqs. (11, 12) described below). This system is defined on N different manifolds M_i ($i = 1, \dots, N$) of similar structure. The i -th manifold is described by Eq. (11) and corresponds to activity of only one neuron with number i (nonzero firing frequency $f_i \neq 0$) and suppression of all other neurons: $f_j = 0, j \neq i$ (here we consider all-to-all coupling scheme):

$$\begin{aligned} \tau \frac{dA_i}{dt} &= c_a f - A_i, \\ f_i &= F_0(I_i^{ext} - \sigma A_i), \\ \tau \frac{dA_j}{dt} &= -A_j, \\ f_j &= 0, j = 1, \dots, N, j \neq i, \end{aligned} \quad (11)$$

where variables $A_i(t)$ and $A_j(t)$ describe an averaged dynamics of the active conductance $g^K(t)_i$ and $g_j^K(t)$, which are responsible for the spike-frequency adaptation in the model (1). f_j stands for instantaneous firing frequency of the i -th neuron, I_i^{ext} describes external current (stimulus) applied to the i -th neuron. Function $F_0(I)$ represents frequency-current relation of the spike-generating mechanism (neuronal firing without adaptation). Due to the spike-frequency adaptation in the presynaptic activity, some of the post-inhibitory neurons may release from inhibitory suppression. Hence, a switch from manifold M_i to the other manifold

M_k is possible. The switch from manifold M_i to the manifold M_k takes place when $f_i \leq f_k^{cr}$ where f_k^{cr} :

$$f_k^{cr} = T_s^{-1} = \frac{g_0}{C_m} \left[\ln \left(\frac{g_0(V_s - V_0) - I_k^{ext} + \tilde{\sigma} A_k}{g_0(V_{thr} - V_0) - I_k^{ext} + \tilde{\sigma} A_k} \right) \right]^{-1}.$$

Therefore, the manifold M_i is bounded in the phase space $\mathbf{A} = \{A_1, A_2, \dots, A_N\}$ by the hyperplanes I_{ik} where $f_i = f_k^{cr}$:

$$l_{ik}, M_i \rightarrow M_k: \quad \sigma A_i = I_i^{ext} - \frac{V_{ahp} - V_s}{V_s - V_{thr}} (I_k^{ext} - \tilde{\sigma} A_k - g_0(V_{thr} - V_0)). \quad (12)$$

Therefore, Eq. (11) in combination with switching conditions (12) describe behavior of the system (1) in the limit of fast and strong synaptic inhibitory coupling. The system (11,12) gives a convenient and natural way of description of non-trivial sequential bursting dynamics, which are likely to appear as a result of interplay between spike-frequency adaptation and mutual inhibition in the network.

2.6 Parameter of heterogeneity in the network

Heterogeneity of the input profile I_i^{ext} is one of the main control parameters in our study. To quantify it, here we introduced parameter I , which describes the difference between the input currents across the neurons:

$$I_i^{ext} = I_0 + \Delta I \frac{N - i}{N - 1}, \quad i = 1, \dots, N. \quad (13)$$

Here I_0 represents a base current, which is equal for all neurons. In contrast, I characterizes the overall difference of external inputs across the network. According to (13) the inputs are equidistantly spaced across the neurons ranging from $I_0 + I$ (for the first neuron) to I_0 (for the last neuron). For an example, the case of $N = 3$ implies

$$I_1^{ext} = I_0 + \Delta I, \quad I_2^{ext} = I_0 + \Delta I/2, \quad I_3^{ext} = I_0. \quad (14)$$

3 Results

The paper is organized as follows: first, we describe the main results of the study using selected and simple nontrivial network configurations. This introductory section aims to provide the reader with enough necessary intuition to continue with the more general analysis described in details later in the manuscript. The next sections apply the method of dimensionality reduction and present direct computer simulations to describe the relations between external stimuli and bursting patterns in the network of coupled inhibitory neurons.

The detailed analysis starts with the description of the oscillatory patterns in a minimal inhibitory network consisting of 2 reciprocally connected neurons. Then we present an analysis of the bursting sequences generated by a network of 3 mutually connected inhibitory neurons and its dependence on the pattern of external stimulation. Based on the results of these two sections, we describe the role of transient processes in the encoding of external stimuli in the Section 3.4. We show that the network tends to generate identical temporal sequences of active neurons for a given feature of the external stimulation pattern. In the last two sections we generalize our results to large networks and test the robustness of the neuronal network dynamics.

3.1 The main results and predictions: an overview

The following section describes the key results and predictions of the paper using basic non-trivial network configurations implementing a conductance-based model (2).

3.1.1 Formation of bursting regimes in the networks of spiking neurons with firing rate adaptation—We start our description with the simplest network configuration, which consists of two coupled neurons with strong and symmetric synapses (Fig. 2a). This case has been extensively studied in (Lewis and Rinzel 2003; Matveev et al. 2007; Daun et al. 2009), but for the sake of completeness we revisited it in our work and focused on the effects of spike-frequency adaptation on the network dynamics. The pair of mutually inhibiting neurons revealed two types of behavior: (i) a complete inhibition of one neuron by the other (Fig. 2d), (ii) an alternating bursting rhythm, which is shown in Fig. 2e. The strength of the internal adaptation current I_{AHP} (parameter g_{ahp} , see Eq. (2)) controlled the type of behavior in the neural circuit. In the first case (Fig. 2d), the spike-frequency adaptation was too weak (because of the small g_{ahp}), such that the active presynaptic neuron spiked with high enough of a firing rate and permanently suppressed the postsynaptic neuron.

In contrast, when g_{ahp} was large, the interplay between intrinsic spike-frequency adaptation and mutual inhibition led to an alternating bursting rhythm shown in Fig. 2e (Assisi and Bazhenov 2012). After a period of activity, the strong adaptation current, I_{AHP} , caused a significant decrease of the firing rate in the presynaptic neuron. This led to the escape of the post-synaptic neuron from inhibition. Hence, neither of the two neurons could suppress activity of its postsynaptic target permanently, which gave rise to an anti-phase bursting rhythm (Assisi and Bazhenov 2012) shown in the Fig. 2e. Further in the Section 3.2 we give a detailed explanation of such bursting rhythm formation in terms of a simple adaptive integrate-and-fire model (1) and a low-dimensional reduction approach given by the system (11,12).

3.1.2 Sequential bursting dynamics during initial transient period reflects properties of external inputs—The intrinsic adaptation current controlled the type of behavior in all-to-all connected networks that contained $N > 2$ inhibitory neurons with strong synaptic connections (Fig. 2b,c). As in the previous case, weak adaptation (small g_{ahp}) led to dominant spiking activity in only one neuron (not shown). When I_{AHP} was strong (large enough g_{ahp}), the interplay between intrinsic spike-frequency adaptation and

mutual inhibition resulted in the sequential bursting dynamics. However, in contrast to the relatively simple alternating bursting in a pair of neurons, the network with more than 2 elements ($N > 2$) exhibited a much more complex behavior with a variety of possible bursting patterns or even non-regular chaotic dynamics (Fig. 2f–i). Despite the complexity, the dynamics of the network always contained a simple and robust invariant feature that carried information about the external inputs I_i^{ext} . As we will explain in detail later, the ranking of the external inputs, I_i^{ext} , always controlled the exact order of burst activation during the initial period after stimuli onset.

It is worth noting that similar networks of inhibitory neurons have been extensively studied before, especially in the context of locomotion and CPG dynamics (Golubitsky et al. 1998; Collins and bifurcation 1992; Nowotny and Rabinovich 2007; Belykh and Shilnikov 2008; Schwabedal et al. 2014; Wojcik et al. 2014). In general, networks of identical neurons display coexisting oscillatory rhythms, which are characterized by distinct phase-locking patterns between individual neurons. For symmetric networks, theoretical results (Golubitsky et al. 1998; Collins and bifurcation 1992; Golubitsky 1985) can predict emerging oscillatory patterns. However, the total number of possible patterns and the exact form of phase-locking relations depend on the size and coupling structure of the network. In contrast to the previous works, we kept the network structure as simple as possible, mimicking densely connected networks of interneurons in the olfactory system of insects (Warren and Kloppenburg 2014; Assisi and Bazhenov 2012). Instead, we introduced asymmetry by means of the heterogeneous external currents applied to the neurons (Eq. 13).

Depending on the degree of heterogeneity $|J|$ (Eq. 14), the network demonstrated a variety of behaviors ranging from a fairly simple bursting wave (for relatively small $|J|$, Fig. 2f) to more complex bursting patterns found for larger $|J|$ in the Fig. 2g–i. It is worth noting, that in the simulation shown in Fig. 2f, the detuning parameter was negative ($I < 0$), meaning that the stimuli were ranked as $I_3^{ext} > I_2^{ext} > I_1^{ext}$ (see Eq. (14)). The latter resulted in the counter-clockwise oriented bursting wave ($3 \rightarrow 2 \rightarrow 1$), which followed the ranking of the external stimuli (we call it below a “correct” sequence of activations). Importantly, the counter-clockwise bursting wave was an attractor (for relatively small $|J|$), meaning that as time increased the network generated the same sequence. However, it is also known that similar network configurations (Fig. 2b) commonly exhibit a prominent multistability (e.g. see (Wojcik et al. 2014)), which manifests itself as a coexistence of a certain number of possible stable solutions (attractors). Indeed, detailed description of similar case (relatively small $|J|$) in Section 3.3 revealed bistability of two possible bursting waves (clockwise and counter-clockwise), which implies that the proper initial conditions are required to initiate the “correct” bursting sequence. That being said, with increasing heterogeneity $|J|$, the attractor that preserves the “correct” bursting sequence (e.g. counter-clockwise for $I < 0$) became dominant and, most importantly, its basin of attraction always included a resting state (the state, which the network reaches in the case of an absence of any external inputs). Therefore, starting from its basic resting state, the network always came to the attractor that reflected the configuration of the external stimuli (for sufficiently small $|J|$).

For larger values of the heterogeneity parameter $|J|$ the resulting dynamics can be fairly complicated, which is shown in the examples presented in Fig. 2g–i. Strongly heterogeneous input profiles led to dynamics where neurons receiving higher input got activated more frequently (Fig. 2g–i). In some cases, this induced non-regular intermittent dynamics shown in Fig. 2g, which was primarily found in conductance-based model (2). High heterogeneity $|J|$ typically induced oscillations with fixed non-trivial ratio of bursting activations. Examples are given in Fig. 2h,i. In both cases shown there, I was positive and sufficiently large, so the third neuron received the smallest stimulus. As a result, the ratio of activations of the third neuron to the first two neurons was 2:3 in panel h ($I = 1.3$) and 1:2 in panel i ($I = 1.75$). We give a more detailed explanation of this dynamical phenomenon using low-dimensional reduction method in the Section 3.3.

The overall picture given by the four simulation cases (Fig. 2f–i) illustrates that the initial period of the neuronal activations always reflected the ranking of the external stimuli I_i^{ext} , meaning that the neurons with larger I_i^{ext} were always activated before the elements receiving lower inputs (see bursts, which are marked by stars). Note that the ranking of I_i^{ext} was opposite for panel F and panels G–I, which resulted in the opposite ordering of the bursting activation. For the simplest case of a relatively small $|J|$, the attractor (the state that the network reaches as $t \rightarrow \infty$) preserved the correct sequence, which is shown in Fig. 2f.

In the more complex cases (larger $|J|$), the “correct” sequence was disrupted due to the large heterogeneities in the input profiles (see e.g. Fig. 2g) or became entangled due to the non-trivial ratios of activations (Fig. 2h,i). However, the initial transient period still showed a clear ordering of the neuronal activations, which allows one to reconstruct the relationships between the external inputs correctly. By transient period (or dynamics) we mean the initial period, which begins at the moment of stimuli onset (vertical arrows in Fig. 2f–i) and lasts for several bursting activations (stars in Fig. 2f–i) before the network goes into the cyclic activity (dynamics on attractor), which can be non-regular or entangled.

In Sections 3.4 and 3.5 we did a comprehensive study and showed that transients robustly reflect the ordering of external inputs in the presence of noise and other perturbations, given that the network was close to its resting state, and its heterogeneity (parameter $|J|$) was large enough.

In the following sections we present a detailed analysis involving simulations of an integrate-and-fire model (1) and a low-dimensional description (11, 12). We would like to emphasize that the method of reduction to the low-dimensional system can be performed in the limit of slow adaptation and infinitely fast and strong inhibition.

Hence, the analysis in the following sections was all done either for the exact limiting case or for the networks that were very close to the limit. Nevertheless, in the current section all examples were constructed for the more realistic dynamics, meaning that the synapses were relatively strong and fast, but we have not implemented the instantaneous shift of the postsynaptic potential (the assumption, that was used for dimensionality reduction). The latter does not allow us to apply the exact reduction to the low-dimensional system, but it

revealed a qualitative agreement between the limiting case analysis and the more realistic simulations, which do not represent the limit.

3.2 Formation of bursting rhythm in a pair of reciprocally inhibiting neurons

We start this detailed description by studying the dynamics of the simplest network, which consists of two reciprocally coupled identical (all parameters are the same) inhibitory neurons (Fig. 2a). We compare the dynamics of the network based on a) a leaky integrate and firing neuron (1); b) Hodgkin-Huxley neurons (2); and c) a reduced low-dimensional system (11, 12) that is defined in terms of the averaged conductance of the slow adaptation current of the model (1). An important advantage of our approach is that the dynamics of the reduced system (11, 12), which describes evolution of the slow adaptation current in each neuron, can be characterized in terms of the critical frequency. The critical frequency was defined as a minimal firing rate of the presynaptic inhibitory neuron that is sufficient to suppress activity of the postsynaptic neuron (see Eq. (12) in Methods). If one neuron could sustain its frequency above the critical firing rate, the system dynamics would be dominated by this neuron the other neuron would be permanently suppressed. If the frequency of firing of an active neuron decreases, e.g., because of adaptation, below the critical frequency, the circuit dynamics switches and the other neuron escapes from inhibition. This leads to the very natural way of describing switching dynamics of the coupled inhibitory neurons.

Similar systems of two coupled inhibitory neurons have been extensively studied (Lewis and Rinzel 2003; Matveev et al. 2007; Daun et al. 2009). However, in our study we focus on the effect of spike-frequency adaptation, which is critical for the following analysis. In the following, the network (1) was considered in the strong pulse-coupled limit: generation of spike in the presynaptic neuron produces rapid decrease of potential $V_{post} \rightarrow V_s$ (V_s is a reversal potential of inhibitory synapse) in the postsynaptic neuron. The latter allowed us to describe the network dynamics in terms of the low-dimensional reduced system (11, 12), however, we also showed that the same behavior takes place in the conductance-based model (2) with relatively strong synaptic inhibition (not necessary in the pulse-coupled limit). The input was the same for both neurons $I_1^{ext} = I_2^{ext}$. The main result of the current section is presented in Fig. 3a where the diagram of different dynamical regimes is plotted in the plane (τ_g, g) for the models (1) and (11, 12). Both parameters τ_g (time scale of recovery from adaptation; larger values correspond to the slower recovery) and g (the magnitude of adaptation associated with a single action potential; larger values correspond to stronger adaptation) are characteristics of the conductance g_i^K (third equation in the system (1)) of the slow adaptation current I_a . Increase of τ_g and/or g leads to strengthening of the spike-frequency adaptation effect.

The structure of the diagram in Fig. 3a is relatively simple: the blue solid curve divides the plane of parameters (g, τ_g) into two areas BR and SP. In the area SP the effect of adaptation is weak, i.e. the neuronal firing frequency decreases insignificantly during continuous spiking and the steady-state firing rate remains high. This led to the kind of dynamics when one neuron totally suppresses activity of another neuron (an example of such dynamics is presented in Fig. 2d). Due to the symmetry, there were two such states – (1) the first neuron is active and inhibits the second one; (2) the second neuron is active and

inhibits the first one. With an increase of g and/or τ_g the system enters the region BR (see Fig. 2a) where adaptation becomes significant. Due to the spike frequency adaptation, one neuron cannot suppress the other one indefinitely.

The frequency of the presynaptic neuron decreases causing the release of the postsynaptic neurons from inhibition. The latter state gave rise to an alternating bursting rhythm (Fig. 3e). A similar principle held for the Hodgkin-Huxley model (2) (see time series plotted in Fig. 2d,e).

While a similar result was reported before using computer simulations (Assisi et al., 2011), here we take advantage of the reduced model (11, 12) to provide a deeper analysis. In the simplest case of $N=2$, the phase space of the low-dimensional system consists of two manifolds M_1 and M_2 of the plane (A_1, A_2) , where $A_{1,2}$ represent mean values of the conductance of the slow adaptive current in the first and second neurons, respectively. Each manifold is described by the system (11). The transition from M_1 to M_2 takes place when the phase point reaches curve l_2 (see Fig. 3b–d). Indeed, on the line l_2 we have $f_1 = f_2^{cr}$ – the frequency of the 1st neuron firing is equal to the minimal frequency that is needed to suppress the 2nd neuron (see Eq. (12)). Beyond l_2 , the firing frequency of the 1st neuron drops below this threshold and the 2nd neuron escapes from inhibition corresponding to transition to the other manifold. In contrast, on the line l_1 (Eq. (12)) the system shifts from M_2 to M_1 .

The dynamics of the model (11, 12), approximating the spiking model (1) in the pulse-coupled limit, can be of two qualitatively different types depending on the strength of the effect of the adaptation current. When the effect of adaptation is sufficiently low (area SP), each manifold M_i contains single globally attracting fixed point FP_i (see Fig. 3b,c)). Each fixed point represents the state when one neuron is active with sufficiently high frequency and completely and indefinitely suppresses activity of another neuron (the time series for qualitatively similar dynamics for HH-type model is shown in Fig. 2d). Average adaptation $A_{1,2}^*$ and frequencies $f_{1,2}^*$ in the stationary states $FP_{1,2}$ can be easily found from the following relations:

$$\begin{aligned} FP_{1(2)}: A_{1(2)}^* &= c_a F_0(I_{1(2)}^{ext} - \sigma A_{1(2)}^*), \quad A_{2(1)}^* = 0, \\ f_{1(2)}^* &= F_0(I_{1(2)}^{ext} - \sigma A_{1(2)}^*), \quad f_{2(1)}^* = 0. \end{aligned} \quad (15)$$

With increase of parameter g , equilibrium point $FP_1(FP_2)$ moves towards the line $l_2(l_1)$ (compare Fig. 3b and c). At some critical value of the parameter, fixed points $FP_{1,2}$ merge with the lines $l_{1,2}$ and move inside the regions of transition between the manifolds (area below l_2 in M_1 and area above l_1 in M_2). In the parameter plane this situation corresponds to the bifurcation curve, which divides areas SP and BR (Fig. 3a). It is worth noting that parameters σ and $\tilde{\sigma}$ changed insignificantly in the plane (g, τ_g) in contrast to the parameter $c_a = g\tau_g$. Shift of equilibrium points $FP_{1,2}$ was mainly caused by the parameter c_a . Therefore, the bifurcation curve (Fig. 3a) can be well approximated by the relation

$\Delta g \tau_g = c_a^*$, where $c_a^* \approx 0.065$ denotes critical value when $FP_{1,2}$ merge with the lines $I_{1,2}$ and leave the manifolds $M_{1,2}$.

In the area BR (Fig. 3a; when the effect of adaptation is strong enough) one neuron cannot indefinitely suppress another, because the resulting (after adaptation) frequencies $f_{1,2}$ are not sufficient for complete inhibition of the post-synaptic neuron ($f_1 < f_2^{cr}$ and $f_2 < f_1^{cr}$). In that case, instead of the globally stable fixed points we observed stable limit cycle L (Fig. 3d) in the system (11, 12). In each manifold M_i trajectories cross the line I_1 (in M_2) or line I_2 (in M_1) sequentially that leads to the switching between the manifolds (Fig. 3d). This dynamics correspond to the sequence of bursting in the circuit of reciprocally coupled neurons (Fig. 3e).

3.3 Formation of bursting sequences in the network of $N = 3$ neurons

In the previous section we described dynamics of two reciprocally coupled inhibitory neurons. For the network with $N = 3$ (the coupling scheme is in Fig. 2b) with identical external currents $I_1^{ext} = I_2^{ext} = I_3^{ext}$ the diagram in Fig. 3a remains correct. When parameters (g, τ_g) are in the area SP (Fig. 3a), one of the neurons always takes over and suppresses the other two neurons in the network. However, when adaptation is relatively strong, any single neuron loses its ability to suppress indefinitely activity in the rest of the network. For $N = 2$, this led to the alternating anti-phase bursting of 2 neurons (Fig. 3e). In the network with $N = 3$ neurons the overall dynamics was more complex and different bursting sequences appeared as a result of strong spike-frequency adaptation and heterogeneity (differences in the strength of external stimuli I_i^{ext}). Therefore, in this section we describe various sequential bursting regimes that appear in the network of $N = 3$ reciprocally coupled inhibitory neurons with relatively strong spike-frequency adaptation (parameters g and τ_g are in the area BR in Fig. 3a). As in the previous section, we assume strong and fast inhibitory synapses (pulse-coupled regime for the system (1)). Below, we show that dynamics of such network strongly depends on the heterogeneity of external afferent inputs I_i^{ext} . To explore this property, we introduced the detuning parameter I according to (14) and focused on the dynamical effects caused by nonidentity of neurons (when $I \neq 0$). Larger values of $|I|$ produced larger difference in the input strength between three neurons. Below we will show that the neuron receiving the largest input has a tendency to spike first in a sequence and also to spike more frequently in a sequence than the neurons receiving weaker inputs. Thus this section prepares us to the main conclusion of the study that the order and pattern of the inhibitory neurons firing may provide information regarding the inputs they receive.

In case of strong reciprocal inhibition and significant spike-frequency adaptation, all dynamical regimes in the network represent sequential bursting modes. Only one neuron captures the activity for any time period and then, due to the decrease of the firing frequency mediated by the spike-frequency adaptation, the activity switches to another neuron in the network. In order to describe all possible solutions, we used the averaged low-dimensional model (11, 12) as well as spiking models (1) and (2).

The main results are presented in the Fig. 4a where a map of the all possible dynamical regimes is plotted in the parameter plane (I, τ_g) ; examples of these regimes are given in Fig. 5d–h. We found that when the effect of adaptation was sufficiently strong (the latter corresponds to sufficiently large value of g), the network exhibited a variety of different bursting modes: from simple bursting wave shown in Fig. 5d to complex bursting sequences when the neuron with the lowest magnitude of input was activated in different ratios (2:3, 1:2, 1:3, etc) in relation to the other neurons of the network (see Fig. 5e–h). Below we provide evidence that the latter type of the bursting dynamics represents typical pattern for the inhibitory networks with spike-frequency adaptation. Importantly, we found that the order of activations in the network is strongly related to the ranking of external stimuli. This finding is discussed in details in the next section. Below we first give a detailed description of the dynamics in the network of 3 inhibitory neurons.

Let us start with the case when the input was the same to all 3 neurons $I = 0$. For $N = 3$ the phase space of the low-dimensional system (Fig. 4b) consists of the three manifolds M_i ($i = 1, \dots, 3$), where each manifold is described by the system (11). As for $N = 2$, dimensions of the phase space represent mean values of conductance of the slow adaptive current in each neuron, (A_1, A_2, A_3) . The system stays on M_i until the phase point crossed one of the surfaces I_{ik} ($k = 1, \dots, 3, k \neq i$) where transition to the manifold M_k takes place. For example on the surface I_{12} the system switches from M_1 to M_2 , on the I_{13} from M_1 to M_3 . The surfaces I_{ik} are defined as hyperplanes according to Eq. (12), where frequency of firing of the presynaptic neuron is equal to the critical frequency that is needed to suppress the postsynaptic neuron, $f_i = f_i^{cr}$. When parameters τ_g and g are in the area SP (Fig. 3a), each manifold M_i contains globally attracting stable fixed point FP_i , which corresponds to the dominating activity of the i -th neuron and complete suppression of the other two neurons.

When the system enters the area BR on the (g, τ_g) plane (Fig. 3a), the points FP_i merge with the planes I_{ik} and leave the manifolds M_i . Therefore, on each manifold M_i the system never reaches a stable fixed point and always crosses a plane I_{ik} after a period of time. In order to describe all possible stable solutions, we used Poincare map. Our methods are adaptation of the technique used in (Wojcik et al. 2014) for theoretical description of the central pattern generator dynamics. As a Poincare section we select the manifold $P = I_{12} \cup I_{13}$ (illustration is in the Fig. 4b). On the surface P the system shifts from manifold M_1 to M_2 or M_3 (the regions of switching either to M_3 or to M_2 are divided by the line F , see Fig. 4b). In the case of $I = 0$ the dynamics of the map $P \rightarrow P$ is illustrated in the Fig. 4c: there are two stable fixed points S_1 and S_2 of the map that correspond to two stable limit cycles in the system (11, 12) (limit cycle S_1 is depicted in the Fig. 4b). Moving along the limit cycle S_1 , the phase point sequentially visits all the manifolds M_i in the direct order $M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow \dots$. In opposite, S_2 corresponds to the reversed sequence $M_1 \rightarrow M_3 \rightarrow M_2 \rightarrow M_1 \rightarrow \dots$. Projection of the map $P \rightarrow P$ on the plane (A_1, A_2) revealed symmetrical basins of attraction of S_1 and S_2 for identical neurons, $I = 0$.

In the following we discuss how the structure of the phase space and the system dynamics change when we introduce heterogeneity I . Remarkably, the network was able to generate large number of different patterns depending on the parameters I (heterogeneity) and τ_g (time scale of adaptation) (Fig. 4a). Different colors in Fig. 4a denote different areas

according to direct simulation of the Eq. (1), and solid blue curves were obtained from the low-dimensional averaged model (11, 12). As one can see, in the parameter plane (I, τ_g) we depicted 6 different areas of distinct network dynamics:

Area A: Coexistence of two simple bursting waves (denoted by S_1 and S_2 in Fig. 4d and a) (see example of spiking dynamics in Fig. 5d). The solution S_1 corresponds to the bursting sequence $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \rightarrow \dots$ and solution S_2 denotes an opposite order of activations. Therefore, the area A corresponds to bistability of two bursting sequences. Two stable fixed points S_1 and S_2 coexist and correspond to the stable limit cycles in the entire phase space of the system. Note that S_1 corresponds to the neuronal activations ordered in the same way as the ranking of external stimuli I_i^{ext} in the ensemble. Indeed, we have $I > 0$ and according to (14) $I_1^{ext} > I_2^{ext} > I_3^{ext}$. Remarkably, with larger asymmetry in the network ($I = 0$) the attractor S_1 becomes dominating (compare basins of attraction of S_1 in Figs. 5a and 4d). With increase of I in the area A (Fig. 4a) stable fixed point S_2 moves towards the line P (Fig. 5a) and, at some critical value of I , merges with the line P and then disappears. Note that P is a line which separates the planes I_{12} and I_{13} on the P .

Area B: The region B is divided into two subareas B' and B'' (see inset in the Fig. 4a). In the area B' , in addition to coexistence of the simple bursting waves $S_{1,2}$ (Fig. 5d), new solution S_3 emerges that corresponds to the non-trivial bursting sequence depicted in the Fig. 5e. The third neuron produces bursts in the ratio 2:3 in comparison to the first two neurons, i.e. during period of 3 consecutive activations of the first neuron there are only 2 activations of the third neuron. On the boundary between B' and B'' (dashed line in the inset) the solution S_2 disappears and in the area B'' two patterns S_1 (simple bursting wave) and S_3 (2:3 bursting) coexist. Mathematical image of the complex 2:3 bursting pattern was a stable period-3 fixed point in the map $P \rightarrow P$ depicted in the Fig. 5b. The construction of the Poincare map shows that the pattern is a stable limit cycle of nontrivial form in the entire phase space of the system. In the area B' all three attractors $S_{1,2,3}$ coexist. In the area B'' we observed bistability of S_1 and S_3 .

Area C: Only S_3 exists (Fig. 5b, e). On the boundary between areas B and C the solution S_1 corresponding to the simple bursting wave disappears and only S_3 remains (2:3 bursting).

Area D: New solution S_4 appears, which corresponds to non-trivial 1:2 bursting regime (Fig. 5f). Due to the large difference between external inputs, I , the third neuron was activated twice less frequently than the first two neurons. Construction of the map (Fig. 5c) revealed that in the area D there is a periodic solution (stable limit cycle) depicted as a stable period-2 fixed point in the dynamics of the map $P \rightarrow P$. In the vicinity of the boundary between areas C and D there is a thin layer where S_3 coexists with new stable period-2 point S_4 (not shown). With small increase of I the point S_3 disappears and only S_4 exists (Fig. 5c).

Area E: Near the left boundary of the region E, 1:2 bursting mode (S_4) disappears and changes into the new solution, which represents 1:3 bursting regime (see Fig.

5g). With further increase of I toward the right boundary of region E, the 1:3 bursting disappears and gives place to the new solutions with even more complex structure such that the relative time of bursting activity of the third neuron decreases and the system subsequently shows multiple regimes of a form 1:n (e.g., see Fig. 5h for 1:5 regime). Note complexity of the bifurcation structures in the area E near the boundaries with the regions D and F. The solutions of 1:n bursting subsequently arise and disappear with certain windows of coexistence (similar to the region B). Finally, near the boundary with region F the period of bursting of the third neuron becomes infinite.

Area F: Because of the large values of the external inputs I_1^{ext} and I_2^{ext} in comparison to I_3^{ext} , the first two neurons totally suppress the third neuron and exhibit alternating bursting rhythm similar to the dynamics depicted in the Figs. 2d, 3e.

In our model, the order of activation of neurons is determined according to the two key factors: (i) the relative magnitudes of external inputs I_i^{ext} and (ii) the state of the adaptation variables $A_i(t)$. Namely, the combinations

$$I_i^e = I_i^{ext} - \tilde{\sigma} A_i \quad (16)$$

(see Eqs. (11), (12)) determine the order of bursting in the network. To understand how the order of activation depends on I , let us consider an initial condition with the 2nd neuron being active (left vertical dashed line in Fig. 5i,k). For relatively small values of I and sufficiently strong adaptation, the 3rd neuron (receiving the smallest input current) recovered from adaptation before the 1st one (receiving the largest current) because the 1st neuron was active more recently and had the stronger adaptation (Fig. 5i, see the right vertical dashed line where $I_3^e > I_1^e$). Therefore, the 3rd neuron fired after the 2nd one and before the 1st one producing a simple bursting wave (Fig. 5k). For larger I the 1st neuron received stronger input and was more active; therefore, it recovered before the 3rd one was ready to escape from inhibition, so the first neuron spiked again ($I_1^e > I_3^e$ on the right dashed line, Fig. 5j).

The 3rd neuron was activated only after two consecutive activation of the 1st neuron when adaptation in the first neuron became strong enough ($I_1^e < I_3^e$, Fig. 5j,l). Further increase of I caused increase of bursting period of the third neuron in area E and complete suppression in the area F (Fig. 4a). Our results are not limited to the model (1) and reduced system (11, 12). We found a similar sequence of regimes for conductance-based model (2) (Fig. 6). For relatively small values of detuning I the system contains two simple bursting waves (Fig. 5a). With increase of I the third neuron exhibited non-trivial activation ratios in comparison to the first two neurons (Fig. 6c–e).

It is worth noting that the conductance-based model has a more complex internal structure in comparison to the reduced models used in our study. Nevertheless, the overall dynamics of the conductance based model was similar to the adaptive integrate-and-fire paradigm in terms of firing rate and adaptation. That is why the overall picture of the dynamical regimes observed in the conductance based model was surprisingly similar to the results obtained

with the reduced models. However, additional nonlinearities and complex internal structure of the conductance based model can induce new effects, which cannot be captured by the simplified models and explained by the low-dimensional system (11). For example, the dynamics in the case of a large heterogeneity has actually a non-regular form, meaning that the inter-burst intervals are not fixed and the entire dynamics is non-periodic (see Fig. 6d,e). This discrepancy becomes prominent when the network is relatively far from the limit of slow adaptation and strong synapses (the limit needed for reduction method). Example is given in the Fig. 2g where the ratio of activations is close to 2:3, but the overall dynamics is intermittent and non-periodic in contrast to the predictions of the reduced models. However, a complete description the dynamics of the conductance-based model goes beyond the scope of this paper.

3.4 The role of transient processes in encoding of external stimuli

Our analyses revealed that input heterogeneity (parameter I) orders activity of the inhibitory network into specific sequences of bursting neurons. Recall that parameter I reflects the differences between external inputs (see Eq. 14) applied to the neurons. Therefore, the spatio-temporal bursting activity can be treated as a simple feature that contains information on the relative magnitudes of the external inputs I_i^{ext} . Below, using low-dimensional system and direct stimulations of the spiking models, we show a direct link between patterns of external inputs and dynamics of the neural network during initial period after stimuli onset. When the input was applied, an initial order of bursting activations in the network always carried information about the relative magnitudes of the external inputs applied to the neurons. Thus, looking at the network dynamics during initial period after stimuli onset, we can predict a pattern of external stimulation.

In the previous section we introduced the detuning parameter $I = 0$ (see Eq. (14)) such that the first neuron always received the largest input current $I_1^{ext} = I_0 + \Delta I$, the next came the second neuron with $I_2^{ext} = I_0 + \Delta I/2$ and the third neuron always had the smallest magnitude I_0 . In the area A on the plane (I, τ_g) (Fig. 3A) the system of three coupled inhibitory neurons revealed co-existence of two stable limit cycles S_1 and S_2 (Fig. 5d) each corresponding to the specific order of neuronal activation: $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \rightarrow \dots$, or $1 \rightarrow 3 \rightarrow 2 \rightarrow 1 \rightarrow \dots$ (reversed). Importantly, for non-zero $I > 0$ the limit cycle S_1 (the solution with activations according to the ranking of I_i^{ext}) becomes dominant: with increase of I the basin of attraction of S_2 shrinks while for S_1 it increases (compare Fig. 4d where $I = 0$ and 5a where $I > 0$). Furthermore, we found that for I the resting state – $V_i = V_0, s_i = 0, g_i^k = 0$ for the system (1) or $A_i = 0$ for the low-dimensional system (11,12) – is always in the basin of attraction of the limit cycle S_1 (Fig. 5a). Thus, starting from the resting state in the area A (Fig. 4a) the neurons always generate bursts in the order $1 \rightarrow 2 \rightarrow 3$. The latter fact is a direct consequence of the order of ranking of the external inputs to the neurons $I_1^{ext} > I_2^{ext} > I_3^{ext}$. We conclude that, in this simple case, bursting sequence in the network follows ranking of the external afferent inputs to the neurons.

Further increase of the difference between input magnitudes, I , led to appearance of the new attractors with non-trivial activations in ratio 2:3 (Fig. 5e), 1:2 (Fig. 5f), 1:3 (Fig. 5g)

and so on up to the region F (Fig. 4a), where only first two neurons are active and the third one is suppressed. To expand our hypothesis regarding the link between external inputs amplitudes I_i^{ext} and spatio-temporal bursting dynamics of the network, below we analyze sequences of bursts generated by the network of inhibitory neurons for generic form of the input

$$I_1^{ext}=I_0+\Delta_1, \quad I_2^{ext}=I_0+\Delta_2, \quad I_3^{ext}=I_0. \quad (17)$$

Figure 7a presents division of the plane of parameters (Δ_1, Δ_2) on the regions with different activation sequences generated by the adaptive integrate-and-fire model (1) in the pulse-coupled limit (the diagram constructed using low-dimensional approximation (11, 12)). Here the sequence means the order in which the neurons produced bursts during initial period after stimuli onset (before stimulation all the neurons were in the resting state).

In the areas B_1 and C_1 the activation order was strictly determined by the ranking of stimuli. In the area B_1 external inputs $I_2^{ext} > I_1^{ext} > I_3^{ext}$ and the sequence of activations was $2 \rightarrow 1 \rightarrow 3 \rightarrow 2$ (Fig. 6c). In opposite, in the area C_1 the stimuli are arranged as $I_1^{ext} > I_2^{ext} > I_3^{ext}$, and the sequence was $1 \rightarrow 2 \rightarrow 3 \rightarrow 1$ (Fig. 7d). We found that increase of the time constant of recovery from adaptation τ_g led to increase of the area $B_1 \cup C_1$, where the network generates basic sequences of activation ordered according to external currents. Thus, in the network with strong adaptation, the relative differences in the input magnitudes $\Delta_{1,2}$ can be large compare to the absolute values of the inputs I_i^{ext} and the system would still generate sequences according to the order of the input magnitudes. For conductance-based model (2), changes Δ_i can be up to 100 % of the base level I_0 , and the ranking property was still preserved. Therefore, in that region of the inputs we observed (a) high reliability of the network responses – different sets of external stimuli I_i^{ext} can produce the same spatio-temporal patterns, and (b) sensitivity to the form of the input – the change of ranking of I_i^{ext} immediately causes the change of the spatio-temporal pattern.

In the areas B_2 and C_2 the overall difference of the inputs received by neurons becomes large and the latter caused more complex sequence of activations when the third neurons was bursting less frequently than the first two neurons (Fig. 7e and f). However, even then the network dynamics displayed a general feature: the order of the *first* activations of the neurons upon stimulation was always formed according to ranking of the input magnitudes. The neuron with the largest input fired first and the neuron with the lowest input always fired after certain number of the bursting periods of the other neurons. An order of activations of the other neurons depended on the relative amplitudes of their inputs I_i^{ext} . Finally, in the area $B_3 \cup C_3$ the overall difference $\Delta_1 + \Delta_2$ was large enough so the first two neurons suppressed the third one at least during the first two activation cycles.

Our analysis predicts that the knowledge of the sequence of bursting in the inhibitory network makes possible to reconstruct the ranking of the amplitudes of the external stimuli the neurons receive. The key component of this prediction is an order of the neurons activation upon stimuli onset. This hypothesis was tested using the elementary network of N

= 3 globally coupled inhibitory neurons. Below we will show that these principles are generic and hold for the larger networks. However, before proceeding to the case of $N > 3$, we will first consider the limitations and stability of this principle against noise.

3.5 Stability against perturbations

In the previous sections we considered an “ideal” case, namely: (a) we assumed that before application of stimuli the network was at the resting state; (b) we assumed noise-free case $\eta = 0$ (see Eq. (1)); (c) we assumed that all the inhibitory connections between the neurons were equal (ideal global coupling). We found that such network can perfectly distinguish between the different configurations of stimuli (stimuli magnitudes ordered in different ways), even when the stimuli are infinitely close to each other (infinitely small $\Delta I_{1,2}$, see (17)). Perturbations to the system in any of the following form: (a) disturbance of the initial conditions, (b) input noise and (c) heterogeneity in couplings reduce the discrimination accuracy. As we show further in this section, the strength of perturbations (e.g. noise intensity) determines critical level of the detuning parameters $\Delta I_{1,2}^{cr}$ (Eq. (17)); above this level the bursting patterns arise according to the ranking of external stimuli as described in the previous section. Thus, we predict that the link between the bursting sequence of the neurons’ activations within the network and the structure of the input to the network is also held for the non-ideal case (e.g., with noise and heterogeneous couplings) if the differences between external inputs I_i^{ext} are sufficiently large.

We consider effect of noisy perturbations on sequence generation in the network of $N = 3$ inhibitory-coupled neurons in the pulse-coupled limit. The pulse-coupled limit in our case implies the equal strengths of inhibition between any two neurons in the network (see section Methods). All parameters of the neurons were identical except for external currents I_i^{ext} . The parameter I was introduced according to Eq. (14); it expresses the level of heterogeneity in the network. Our analysis is split into two parts: first, the network dynamics is modeled without external stimuli ($I_i^{ext} = 0$), but under the action of noise. This corresponded to relaxation to the resting state with some stochastic fluctuations. Second, the external inputs I_i^{ext} were applied, leading to sequential bursting of the neurons. Figure 8a shows dependence of the probability $P(\eta)$ that the network generates sequence of bursts ordered according to the ranking of external stimuli. The probability depends on the noise amplitude η . Analysis of $P(\eta)$ dependence (Fig. 8a) includes few different combinations of the input amplitudes. For $I_1^{ext} > I_2^{ext} > I_3^{ext}$, the $P(\eta)$ denotes probability of the event that the network generates sequence $1 \rightarrow 2 \rightarrow 3$ or sequence $1 \rightarrow 2 \rightarrow 1 \rightarrow 3$ (sequences that carry information on stimulation pattern, Fig. 7d,f). We found that the probability decreased (starting from $P = 1$ for $\eta = 0$) with increase the noise intensity. Importantly, for all I (different curves) the probability stayed close to 1 for a certain range of η . The latter means that up to a certain critical value of noise $\eta < \eta_{cr}$ the network dynamics was robust and the probability was high that resulting pattern was formed according to the ranking of external stimuli. Figure 8b plots the critical value η_{cr} (defined for $P(\eta_{cr}) = 0.95$) depending on the heterogeneity parameter I . We concluded that increase of heterogeneity in external currents I_i^{ext} increases the probability of discrimination of different types of external stimuli (discrimination of different rankings of external currents) in presence of noise.

In above, we considered the model when all synaptic couplings in the network had the same strength. The latter means that $G_{ij} = G_0$ (equal for all synapses) in (1), (2). To study how variability of the coupling strength affect the bursting pattern, we calculated statistics of generation of the bursting sequences by different networks where coefficients G_{ij} were random values uniformly distributed in the interval $[G_0(1 - \sigma), G_0(1 + \sigma)]$. Figure 8c and d show dependence of the probability P (the probability of generating the sequence of bursts ordered according to external stimuli) on the parameter G_0 (mean value of distribution) for different values of σ (spread of distribution). In the Fig. 8c we set $I = 100$ and in the Fig. 8d we used $I = 300$.

Increase of the range of the coupling strengths σ decreased the probability P . However, increase of the mean inhibition G_0 compensated for the heterogeneity of couplings and led to increase of the probability P . Furthermore, comparing plots in Fig. 8c and d, we found that increase of I also led to upturn of the probability P . Therefore, we concluded that heterogeneity of the strength of synaptic couplings decreases ability of the network to discriminate external inputs. These adverse consequences of the heterogeneity can be compensated by increase of the averaged strength of inhibition in the network and/or by increase of the difference in external inputs I .

3.6 Generalization for large networks, $N > 3$

In this section we investigate the network dynamics for a general case of more than 3 neurons, $N > 3$, and discuss an application of the described dynamical mechanisms to the problem of the information coding in the olfactory system.

In many systems activation of the sensory receptor neurons can be described by sigmoid function of the input (denoted as C_i in Fig. 9a) (Ito et al. 2009). In olfactory system, e.g., different types of the olfactory receptors have different sensitivity for a given odor that can be described by the relative shift of the activation curves. In insects, the axons of the olfactory receptors project to the antennal lobe (AL) where they make connections within populations of the excitatory projection neurons (PNs) and inhibitory local neurons (LNs) (Leitch and Laurent 1996). Feedback inhibition from LNs to PNs leads to odor triggered LFP oscillations in the AL (Bazhenov et al. 2001). LNs also form inhibitory connections to each other, thus forming a network of the kind we considered in this study. We showed previously that the inhibitory connections between LNs determine pattern of sequential LN activation and also that this pattern determines synchronization properties of the postsynaptic excitatory PNs (Assisi et al. 2011; Assisi and Bazhenov 2012). This study, however assumed identical input to all of the inhibitory neurons of the AL network.

Below we consider a network of $N = 10$ inhibitory AL neurons receiving different inputs $I_i^{ext} = I_0 + \Delta_i + \eta \xi_i$ from receptor neurons. While this model has not been designed to describe in details dynamics of the AL, it can provide some important insights about patterns of activity in the densely connected population of the olfactory neurons. We tested three different stimuli (different by concentration) denoted by S_1 , S_2 and S_3 (Fig. 9b). For the sake of simplicity for each stimulus we assumed an equidistant profile of the inputs to the AL inhibitory neurons. To simulate effect of noise, we introduced the term $\eta \xi_i$ corresponding to

the fluctuations in the afferent input, that was given by a white noise process with the following properties: $\langle \xi(t) \rangle = 0$, $\langle \xi(t) \xi(t - t_0) \rangle = \delta(t - t_0)$.

For the stimulus (S_1) with a “moderate” concentration, distinct olfactory receptor types responded with different and distinct firing rates (no saturation), thus providing a large dynamical range of the inputs (differences in I_i^{ext}) to the inhibitory neurons (LNs of the AL) (Fig. 9a,b, green line). The dynamics of the network simulated by the conductance-based model (2) is shown in the Fig. 9c. Relatively large differences in I_i^{ext} of the applied inputs resulted in a clear bursting pattern – the neurons were activated according to the ranking of external stimuli I_i^{ext} . Because of the noise in the system, this precise dynamics degraded over time, so the following sequences displayed less agreement with the input ranking. Thus, in agreement with our theoretical analysis, initial (upon stimuli onset) sequence of the bursts generated by the network reflected ranking of the inputs and allowed to reconstruct relative magnitudes of the external inputs from observed patterns of activity.

When the odor intensity was high (S_2), olfactory receptors responded at the high firing rate, but within a narrow range of the amplitudes across receptor types – small dynamical range of the inputs to the LNs of the AL (Fig. 9a, b, blue line). In the latter case the outputs of the receptors were saturated (“upper” part of the sigmoid, see Fig. 9a and b, blue line). As we showed previously, the sequence generation in the network with a small difference in the intensity of the inputs is unstable against noise, so the network dynamics did not reflect well the input ranking (Fig. 9d).

Expectedly, small odor concentration S_3 (Fig. 9a) resulted in a small and narrow distribution of the inputs I_i^{ext} to LN neurons (Fig. 9a,b, red line), which didn’t evoke any significant response in the LN network (data not shown).

We conclude that while proposed link between the dynamics of the inhibitory network and the structure of the input can fall apart for the noise networks with a small difference between input amplitudes, it is still held in the the networks when the input pattern has enough dynamical range to overturn effects of noise.

4 Discussion

The insect olfactory network is a highly efficient computational system; in the locust antennal lobe a relatively small network of excitatory projection neurons and local inhibitory interneurons (~ 1200 cells total) can effectively discriminate a very large number of the chemical stimuli, which are represented by the semi-static spatial patterns of approximately 50,000 olfactory receptors (Joseph et al. 2012). It has been proposed (Laurent 2002; Friedrich and Laurent 2004) that the olfactory system uses the combinatorial complexity of the spatio-temporal patterns of the neuronal circuit activity to create a large coding space for olfactory stimuli. Indeed, in many types of the neuronal networks external inputs evoke stimuli-specific sequences of the metastable states where each state is characterized by a group of active and spiking neurons (Laurent and Davidowitz 1994; Laurent et al. 1996; Friedrich and Stopfer 2001; Friedrich and Laurent 2004; Jones et al. 2007). The structure

and the order of activations of the neuronal groups drastically depend on the external stimulation making it possible to effectively discriminate between different sensory inputs.

Networks of the inhibitory interneurons appear to be a crucial component of the sensory processing in many systems (Steriade and Deschenes 1984; Kisvarday et al. 1993; Von Krosigk et al. 1993; Golomb et al. 1994; Freund and Buzsáki 1996; Rinzel et al. 1998), including synchronization and pattern formation in the insect olfactory system (Bazhenov et al. 2001; Rabinovich et al. 2006; Assisi et al. 2011; Assisi and Bazhenov 2012). Intracellular recordings made *in vivo* from locust AL projection neurons (PNs) have revealed that individual PNs transiently phase-lock with population oscillations at times that vary with the stimulus – a phenomenon called transient synchronization (Laurent et al. 1996). This fine temporal structure is stable over trials and is different for different PNs (Laurent et al. 1996; Wehr and Laurent 1996; Bazhenov et al. 2001). This temporal structure appears to arise, at least in part, from circuit interactions within the AL. Indeed, in the locust, pharmacologically blocking the inhibitory GABA-A receptors in the AL by injecting picrotoxin eliminates population oscillations, and leads to a breakdown in the specificity of odor responses in the beta-lobe interneurons, which are followers of the Kenyon cells (KCs) of the mushroom bodies (Stopfer et al. 1997; MacLeod et al. 1998). Further, behavioral experiments with honeybees demonstrate that picrotoxin-induced desynchronization of the AL neurons causes a loss of precise odor discrimination (Stopfer et al. 1997; Hosler et al. 2000).

Evidence for odor-evoked spatio-temporal patterns of neuronal activity is not unique to the insect; in salamander OB complex spatio-temporal patterns of activity were revealed by voltage-sensitive dye imaging (Cinelli and Kauer 1992; Cinelli et al. 1995). Recordings from the turtle OB revealed that different assemblies of cells are activated during different cycles of field oscillations, supporting the hypothesis that odors are encoded by the spatio-temporal patterns (Lam et al. 2000). Thus, the AL and the OB appear to process, or reformat, the olfactory information from a diverse population of receptors into a spatio-temporal code.

In our previous computational studies of transient synchronization of the olfactory neurons, we focused on the intrinsic network dynamics and largely ignored effects of the input heterogeneity across sensory neurons (Assisi et al. 2011; Assisi and Bazhenov 2012). The questions remained (a) what is a potential computational complexity of such network dynamics; (b) how do the spatio-temporal patterns of the neuronal circuit activity reflect information on the external stimuli distributed in the network; (c) whether observed dynamics is a specific feature of the olfactory-type neural networks or can it be generalized beyond insect antennal lobe. In the current work we address these questions using a theoretical description of sequential bursting dynamics in networks of inhibitory neurons with spike-frequency adaptation.

Starting with a “minimal” reduced model that has a relatively simple mathematical structure and expending to the Hodgkin-Huxley type models, we showed that the interplay between the spike-frequency adaptation mechanism on a cellular level and reciprocal inhibition on a network level leads to formation of sequential bursting dynamics. We showed that the sequence of neuronal firing within a network predicts the ranking of the input amplitudes to

these neurons. This principle remains even in the presence of noisy fluctuations and variability of the network connectivity structure – the network has a strong tendency to organize the firing sequences according to the amplitude arrangements of the stimuli. Our study predicts that the inhibitory network may decode the information about stimuli intensity by converting it to temporal sequences and is able to generate combinatorial number of different patterns creating a large coding space for a large (in comparison to the network size) number of the distinct types of stimulation. This dynamics is robust, the sequences are preserved even for significant fluctuations in the input intensity as long as the ranking of the stimuli intensities remains unchanged.

A minimal set of conditions that are necessary for this dynamics to operate – reciprocal inhibitory coupling and spike frequency adaptation – is not unique to the locust olfactory system. Recent experimental studies of the cockroach antennal lobe neuronal network (Warren and Kloppenburg 2014) revealed that 95 % of the investigated type I local interneurons have reciprocal inhibitory connections. Furthermore, voltage traces of the interneuron activity indicate a presence of spike-frequency adaptation. While fast spiking inhibitory interneurons in the neocortical circuits do not show strong spike adaptation, other common classes of interneurons – somatostatin-expressing, low threshold-spiking (LTS) (Beierlein et al. 2003) and Martinotti (Wang et al. 2004) cells – adapt and, therefore, also possess basic properties necessary for the sequence formation. In thalamus, spike frequency adaptation mediated by Ca^{2+} dependent K^{+} currents (Bal and McCormick 1993) is observed in the reticular thalamic neurons that form a densely interconnected GABAergic network (Steriade et al. 1997).

In the cortical and hippocampal networks, inhibitory interneurons form dense connections to the pyramidal neurons (PYs) (Yoshimura and Callaway 2005). These connections create a feedback inhibitory loop responsible for synchronized firing (Buhl et al. 1998). The importance of the lateral inhibitory connections for the network oscillations was previously described in the thalamic reticular nuclei (Wang and Rinzel 1993; Golomb et al. 1994; Bazhenov et al. 1999) and hippocampus (Wang and Buzsáki 1996). It was suggested that lateral inhibition is important for synchrony of cortical beta oscillations (Jensen et al. 2005). In contrast to the AL network where inhibitory local neurons project broadly within entire AL, in the neocortex the inhibitory interneurons form primarily local connections to their neighboring neurons. This structure promotes local wave propagation (Gabriel and Eckhorn 2003).

Inhibitory networks have been extensively studied theoretically in the context of rhythmogenesis (Ermentrout 1992; Wang and Rinzel 1992; Golomb et al. 1994; Van Vreeswijk et al. 1994; Terman et al. 1998; Lewis and Rinzel 2003; Belykh and Shilnikov 2008; Schwabedal et al. 2014; Wojcik et al. 2014) and pattern formation (Ermentrout and Kopell 1994; Rinzel et al. 1998; Golomb and Ermentrout 2001; Pinto and Ermentrout 2001) for different network configurations and intrinsic cell properties. The novelty of our study is linking properties of the external stimuli to the inhibitory network dynamics. In contrast to the previous studies, we focused on the question of how heterogeneity in the input to the network affects bursting patterns and we found invariant dynamical properties (the order of bursting activations) reflecting the structure of the external stimuli.

Our results are based on the study of the densely connected networks where synapses are sufficiently strong and reciprocal. Alternatively, sequential bursting dynamics can appear due to the asymmetric inhibitory connections (Nowotny and Rabinovich 2007; Komarov et al. 2009; Komarov et al. 2009). In these models, the order of bursting is determined by the features of the connectivity structure, such as low strength or absence of synapses. The latter makes the system less sensitive to the form of external stimulation, because the neurons activate according to the form of synaptic connectivity.

Our study can be directly generalized to larger networks of the inhibitory neurons that can be divided into populations of neurons with no connections between neurons within each population but inhibitory connections between neurons belonging to the different populations. The dynamics of such network can be reduced using graph coloring (Assisi et al. 2011) to the minimal number of the interacting populations. In this case, an entire population of a specific “color” would fire together and a sequence of firing could still be determined by the ranking of the inputs to the populations of the interneurons of different “color”.

Sequential activation of neurons has been observed in the neocortex and hippocampus during behavioral tasks and during sleep. In the hippocampus, the spatial location of a rat is shown to activate a specific group of neurons called place cells (O’Keefe and Dostrovsky 1971). When the rat traverses a path in space a specific sequence of the place neurons is activated. There is growing evidence that learning a trajectory in space involves reactivation of these sequences even when the animal is not physically traversing the path. Replay of spike sequences has been shown during sleep and awake states in the rat hippocampus (Louie and Wilson 2001; Lee and Wilson 2002; Foster and Ma 2006) and the other brain areas including the primary visual cortex (Ji and Wilson 2007). In humans, behavioral studies have now established that sleep increases memory recall (Diekelmann and Born 2010), most likely through the replay of spike sequences. One of the key criteria for the propagation of activity in a feed-forward manner is the existence of a synchronous group of neurons – a pulse of activity that can propagate undiminished across the network (Diesmann et al. 1999). Inhibition can corral principal neurons into the transiently synchronous ensembles. Transitions between different active groups of the inhibitory neurons, as predicted by our study, can lead to transition from one group of synchronized principal neurons to another thus manifesting propagation of activity.

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Fig. 1.

Method of reduction from oscillatory spiking model to the low-dimensional averaged system

(single neuron). **a:** Plots show dependences $\varepsilon(f) = \frac{\tau_g - \tau(f)}{\tau(f)}$ for different values of τ_g (see legend) and for fixed $g = 0.25$. **B:** Plots show an accuracy of the linear approximation

$\tilde{I} = \sigma \langle g^K \rangle_{T_{isi}}$. Function $\gamma(f)$ defined in Eq. (9) represents the relative error of the linear approximation plotted as a function of firing frequency f . **C, D:** The time series of the model (1) (in panel **c**) and model (5) (in panel **d**) are presented. One can see similar behavior of the spiking and low-dimensional averaged models. Parameters: in the panel **C** we used $g = 0.25$, $\tau_g = 0.5$, $I^{ext} = 800$; in the panel **d** for simulations we used $\sigma = 29.5$, $c_a = 0.125$, $\tau = 0.5$ (obtained from reduction procedure) and $I^{ext} = 800$. **e:** Relative error for frequency

$\delta_f = |1 - f/T_{isi}^{-1}|$ and for slow adaptation variable $\delta_{g^K} = |1 - A/g^K|$

Fig. 2.

Network structures (panels **a–c**) and sequential bursting dynamics in the network of inhibitory neurons modeled by Hodgkin-Huxley-type model (2). **a,b**: Small microcircuits that consist of two (**a**) and three (**b**) mutually coupled inhibitory neurons. Here large open circles represent neurons. Solid lines with filled circles depict inhibitory synapses. **c**: Schematic representation of relatively large network consisting of 10 neurons is shown. Solid lines depict reciprocal inhibitory synapses (all-to-all coupled structure). **d**: One neuron is active and completely inhibits activity of the other neurons (area SP in Fig. 3a). **e**: Alternating bursting rhythm caused by increase of impact of the adaptation current (area BR in Fig. 3a). Parameters: in **D** $g_{ahp} = 0.1$, in **I** $g_{ahp} = 0.3$. In both cases $I_{1,2}^{ext} = 2.2$. **f**: Simple bursting wave in the network of 3 mutually inhibiting neurons (panel **B**) is shown. $I_0 = 2.6$, $I = -0.4$. **g**: Non-regular behavior induced by strong heterogeneity in the network. $I_0 = 2.2$, $I = 0.6$. **h,i**: Strong difference in external inputs induced complex bursting, characterized by non-trivial activation ratio: 2:3 for panel **h** ($I = 1.3$) and 1:2 for panel **i** ($I = 1.75$). Stars denote bursts during initial transient period, which reflected ranking of external inputs: $I_3^{ext} > I_2^{ext} > I_1^{ext}$ for panel **g** and $I_1^{ext} > I_2^{ext} > I_3^{ext}$ for panels **G–I** (numeration from top to bottom). Vertical arrows indicate the stimuli onset. The network had been located in the resting state before inputs were applied. For panels **F–I** $G_{ij} = 10$, $\tau_{Ca} = 200$, $g_{ahp} = 0.4$. In all panels vertical scalebars depict 100 mV, horizontal scalebars denote 50 ms in panels **D–G**, 100 ms in **H** and 150 ms in **I**.

Fig. 3.

Dynamical properties of a pair of mutually inhibiting neuron. **a**: Regions of the different dynamical regimes are shown for the circuit of two reciprocally inhibiting identical neurons (Eq. (1)). Area BR: regime of alternating bursting behavior (time series is shown in panel **e**). Area SP: regime when one neuron suppresses the activity of the other neuron (time series are given in Fig. 2d). **b–d**: Phase portraits of the system (8) are shown. Thick solid or dotted lines correspond to the phase trajectories (solid for the manifold M_1 and dotted for the manifold M_2). Thin solid lines are the lines of transition from one manifold to another: on the line l_1 frequency $f_2 = f_1^{cr}$ and above l_1 the system makes switch from M_2 to M_1 , on the line l_2 frequency $f_1 = f_2^{cr}$ and below l_2 there is a transition from M_1 to M_2 . The phase portraits in panels b–d correspond to the points p_1 , p_2 and p_3 on the $(\Delta g, \tau_g)$ plane (panel **a**). Parameters used in the averaged model (obtained by the averaging procedure described in The “Methods”) are the following: in **b** $\sigma = 28.04$, $\tilde{\sigma} = 26.19$, $c_a = 25 \times 10^{-3}$; in **c** $\sigma = 28.37$, $\tilde{\sigma} = 26.53$, $c_a = 50 \times 10^{-3}$; in **d**: $\sigma = 28.87$, $\tilde{\sigma} = 26.17$, $c_a = 100 \times 10^{-3}$; **e**: The time series of the low-dimensional (11, 12) and integrate-and-fire model (1) in the pulse-coupled limit for $\tau_g = 0.5$, $g = 0.2$, $I_{1,2}^{ext} = 800$ (point 3 in Fig. 3a)

Fig. 4.

Analysis of the network of 3 reciprocally coupled inhibitory neurons. **a:** Different regions in the parameter plane (I, τ_g) are shown for the adaptive integrate-and-fire model (1) in the pulse-coupled limit (by color code) and for the low-dimensional model (11,12) (blue solid lines). Parameters: $g = 0.25, I_0 = 800$. **b:** The phase space of the model (11, 12) is shown. The point O is the most distant point on the plot. The area in the center of the plot is an intersection of the all manifolds $\cap M_i$, which is bounded by the parts of the planes l_{ik} (shown by solid surfaces with different colors). Three curves with arrows correspond to the phase trajectories. Blue curve is in the manifold M_1 , red in the M_2 and green in the M_3 . Starting in M_1 the trajectory stays here until it crosses the hyperplane l_{12} where it switches to the manifold M_2 . Parameters: $\tau = 0.9, I_0 = 800, I = 0, g = 0.25$. **c:** An example of the mapping of $P = l_{12} \cup l_{13}$ to itself. X_0 and Y_0 are two different sets of initial conditions. X_1 and Y_1 are images of X_0 and Y_0 correspondingly after one iteration of the map. Line F is a line which separates planes l_{12} and l_{13} . Below F the system switches to M_3 , above it to M_2 (see the panel B). $S_{1,2}$ – two stable fixed points of the map. Here all neurons are identical with the same external currents ($I = 0$). Parameters are the same as in **b**. **d:** Projection of the map $P \rightarrow P$ on the plane (A_1, A_2) . The basins of attraction of S_1 and S_2 are indicated (gray area is for the stable fixed point S_2) for identical neurons $I = 0$. Due to identity of the neurons, the structure of the basins of attraction is symmetric. Parameters are the same as in **B**.

Fig. 5.

Phase planes and voltage traces of the network of 3 reciprocally coupled inhibitory neurons. **a–c:** Stable fixed points of the Poincare map $P \rightarrow P$ (projected to the plane (A_1, A_2)) are shown for different areas of the parameter plane (I, τ_g) (see Fig. 4a) in the low-dimensional system (11, 12). **a:** Area A (Fig. 4a). Two stable fixed points S_1 and S_2 coexist. Gray area is the region of attraction of the stable fixed point S_2 . Each stable fixed point corresponds to the bursting travelling wave in the network (time series are shown in the panel D). **b:** Area C (Fig. 4a). Here period-3 fixed point S_3 describes complex bursting pattern when the third

neuron fires at the ratio 2:3 to the first two neurons (see time series in the panel **e**). **c**: Area D (Fig. 4a). Stable period-2 fixed point S_4 corresponds to the 1:2 bursting pattern (time series is in the panel **f**). **d–f**: Traces $V_i(t)$ are shown, which correspond to the stable fixed points depicted in the panels **a–c** (integrate-and-fire model (1)). **g,h**: Time series of the complex 1:3 (in the panel **G**) and 1:4 (in the panel **h**) bursting patterns in the area E (Fig. 4a) near the boundary with region F. Parameters: for all plots $\tau_g = 0.9$, $g = 0.25$, $I_0 = 800$. **A,D**: $I = 90$; **b**: $I = 140$; **c,f**: $I = 180$; **G**: $I = 250$; **h**: $I = 270$. **i–l**: The plots explain non-trivial bursting activations depicted in Fig. 5e–h. **i,k**: The overall averaged currents I_j^e (see Eq. (16)) and instantaneous firing frequencies f_i are plotted as a function of time for the system (11, 12) in the case of simple bursting wave in the network. Parameters: $I_0 = 800$, $I = 50$, $g = 0.25$, $\tau = 0.9$. **j,l**: The same as in the panels **i,k** but for larger detuning parameter $I = 160$.

Fig. 6.

Complex bursting patterns in the conductance-based model (2) in the network of 3 reciprocally inhibiting neurons. **a:** Coexistence of two travelling waves similar to the case depicted in Fig. 5a,d (area A in the Fig. 4a). **b:** 2:3 bursting pattern similar to the case depicted in Fig. 5b,e (area C). **c:** 2:1 bursting pattern similar to the case depicted in Fig. 4C,F. **D:** 1:3 bursting pattern. **e:** Increase of I leads to irregular bursting patterns with rare activations of the third element. Parameters: for all calculations we use $g_{ahp} = 0.4$, $I_0 = 2.0$, $G_{ij} = 20$ (**a**) $I = 0.3$; (**b**) $I = 1.5$; (**c**) $I = 1.7$; (**d**) $I = 2.0$;

Fig. 7.

Sequences of bursts in the network of $N=3$ neurons predict pattern of external inputs (Δ_1, Δ_2) . **a:** Different regions on the plane of parameters (Δ_1, Δ_2) are shown for the integrate-and-fire model obtained using low-dimensional model (11, 12). Parameters: $I_0 = 800$, $g = 0.25$, $\tau_g = 0.6$. **b:** The same as in the panel A but for the conductance-based model (2). Parameters: $g_{ahp} = 0.4$, $I_0 = 2.0$, $G_{ij} = 20$. **c-f:** The neuronal dynamics modeled by the system (1) (in the pulse-coupled limit) in different regions on the plane (Δ_1, Δ_2) (panel **a**)

Fig. 8.

Robustness of the network dynamics. **a:** Probability P of generation of the correct sequence (which carries information about input pattern) in the network of $N = 3$ spiking neurons modeled with the integrate-and-fire system (1) in the pulse-coupled limit. Different labels on the plot denote different values of ΔI . The dashed black line denotes level $P = 0.95$. η is an amplitude of white Gaussian noise. **b:** Dependence of η_{cr} (defined as $P(\eta_{cr}) = 0.95$) on ΔI is shown. For A and B external stimuli are: $I_1^{ext} = 800 + \Delta I$, $I_2^{ext} = 800 + \Delta I/2$, $I_3^{ext} = 800$. Other parameters are following: $\tau_g = 0.9$, $g = 0.25$, $s = 10$. **c,d:** Plots show dependence of the probability P on G_0 . The coupling constants G_{ij} were distributed randomly in the range $[G_0(1 - \sigma), G_0(1 + \sigma)]$ (values of σ are shown in the legend). In the plot C $I = 100$, in the plot D $I = 300$. In both plots $g = 1.5$, $\tau_g = 1.5$

Fig. 9.

Dynamics of the inhibitory network (N=9) in the context of the information processing in the olfactory system. **a:** Response curves of the different olfactory receptor neurons (different curves) to a given odor as a function of an odor concentration (x-axis). **b:** Inputs I_i^{ext} from different olfactory receptor neurons to the inhibitory LNs of the AL network model are shown as a function of the LN index in the network (x-axis). The plot illustrates three different stimuli $S_{1,2,3}$. S_1 corresponds to the moderate odor concentrations and the large difference in the receptor neurons firing rates. S_2 and S_3 correspond to the strong and weak odor concentrations, respectively. **c,d:** Spatio-temporal network dynamics are plotted for the different stimuli S_1 (panel c), S_2 (panel d). Parameters of the model (2): $\alpha_s = 10$, $\beta_s = 0.5$, $\alpha_{Ca} = 2 \times 10^{-4}$, $G_{ij} = 20$, $\eta = 0.1$