Variable Synaptic Strengths Controls the Firing Rate Distribution in Feedforward Neural Networks

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Abstract  Heterogeneity of firing rate statistics is known to have severe consequences on neural coding. We previously developed theoretical methods to understand how two attributes (synaptic and intrinsic heterogeneity) interact and alter the firing rate distribution in a population of integrate-and-fire neurons with random recurrent coupling. Building upon those results, we adapt this framework and apply it to a delayed feedforward spiking network to demonstrate how these models can qualitatively capture the modulation of firing rate heterogeneity in data from sensory neurons. Recent experimental recordings in weakly electric fish indicate that the distribution of superficial pyramidal cell firing rates in the electrosensory lateral line lobe (ELL) depends on the stimulus, and also that network inputs can mediate changes in this distribution. The developed theory captures this data and specifically demonstrates how heterogeneous neural attributes alter firing rate heterogeneity, accounting for the effect with various sensory stimuli. This leads to a prediction about how the strength of the effective network connectivity is related to intrinsic heterogeneity: the strength of the delayed feedforward is positively correlated with excitability (threshold value for spiking) with low firing rate heterogeneity and is negatively correlated with excitability with high firing rate heterogeneity. With computational models, we demonstrate that neural attributes do not interact in a simple manner but rather in a complex stimulus-dependent fashion to control neural heterogeneity and to ultimately shape population codes.

Keywords  Threshold Heterogeneity · Synaptic Strength Variability · Firing Rate Heterogeneity · Feedforward network · Leaky Integrate-and-Fire Neurons · Weakly Electric Fish

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Introduction

The mechanisms and features of neural networks that enable efficient sensory coding is an important topic with many advances stemming from a combination of experiments and computational modeling. In a population of neurons, understanding how sensory signals are encoded and transmitted to higher areas of the brain is especially challenging given that neurons, even in early stages of processing, are known to be stochastic and have heterogeneous attributes. The structure and distribution of this heterogeneity will thus determine how the population of neurons jointly encode a stimulus. Firing rate heterogeneity has been shown to have consequences on neural coding in the olfactory bulb (Padmanabhan and Urban, 2010; Tripathy et al., 2013), and in models of the visual system with diverse orientation tuning curves (Shamir and Sompolinsky, 2006; Chelaru and Dragoi, 2008), and a variety of other systems (Georgopoulos et al. 1986; Marsat and Maler, 2014; Ahn et al., 2014). In general, the firing rate heterogeneity is known to affect important information-theoretic measures of coding such as the Fisher information and mutual information (Kay, 1993). This quantity is a significant measure for systems that code signals based on rate, or the total number of spikes. Although we do not focus on the potential impact of higher order spiking statistics, firing rate heterogeneity has a direct impact on the way the population encodes sensory signals. The primary focus of this paper is on the firing rate heterogeneity (distribution) of specific pyramidal cells in a delayed feedforward network that replicates the overall structure of the Electrosensory Lateral Line lobe (ELL) of weakly electric fish.

The weakly electric fish is a well established model of sensory processing that continues to provide powerful insight into the neural dynamic of sensory coding. The ELL is particularly well understood (Maler, 2009), it is the sole gateway from the peripheral electrosensory receptors to higher sensory areas. The principle cells of this network – pyramidal cells – receive direct input from receptors and project to the next level of sensory processing. A subset of pyramidal cells (the so-called superficial and intermediates) will be the focus of this study because they receive both the direct feedforward inputs and a large set of inputs from parallel fibers projections. Parallel fibers originate for the caudal lobe of the cerebellum which is driven by input from another subset of ELL pyramidal cells, deep pyramidal cells. Therefore, although this parallel fiber input to superficial pyramidal cells is traditionally described as feedback, it is an open loop configuration and thus can be regarded as an indirect delayed feedforward input. Pyramidal cell response heterogeneity (even within the superficial subset) has been shown to be important for coding of different types of natural signals (Marsat and Maler, 2010; Marsat et al., 2012). Network dynamic, in particular parallel fiber input, can influence heterogeneity and correlation among responses (Litwin-Kumar et al., 2012). A recent dataset from our lab (see Fig. 1B) indicates that heterogeneity can be modulated in a stimulus-dependent manner so as to shape the population code (Marsat et al., 2014). Specifically, low frequency stimuli typical of male-male aggressive interaction elicit population responses with low firing rate heterogeneity whereas high frequency stimuli typical of male-female interactions and courtship lead to higher heterogeneity. Low or high frequency sinusoidal amplitude modulations of the fish’s electric field are present during any interaction with conspecific. These sine waves are thus the natural background signal that set the neural dynamic in a specific mode, thus influencing the processing of transient communication signals. This observed change in heterogeneity of the population raises a question: how can a single population of cells change its response heterogeneity instead of the heterogeneity being a fixed attribute of the population? A simple answer would be that the inputs to the cells change as a function of the stimulus; another answer is that input heterogeneity could interact with intrinsic properties to produce complex changes in response heterogeneity.

Here we consider two sources of firing rate heterogeneity: intrinsic and network. Many intrinsic factors influence the firing rate of a cell such as ion channel composition or cell morphology. Arguably, the most central parameter that dictates firing rate is the threshold of the cells since low threshold will directly cause high firing rates and vice versa. Threshold heterogeneity has been shown experimentally in cortical cells (Azouz and Gray, 2000) and has crucial effects in the electrosensory system (Middleton et al., 2009) and others (Priebe and Ferster, 2008). We therefore use threshold as the source of intrinsic heterogeneity
across our population of cells. Note that a cell’s threshold is itself dictated by a variety of factors but it is not our goal to detail the underlying molecular dynamic at play. Network heterogeneity refers to any aspect of the network inputs that can influence the cell’s firing. Here again we focus on the simplest parameter of network input affecting a cell’s firing: input strength (Marder and Goaillard, 2006; Chelaru and Dragoi, 2008). Input strength is determined by many physiological parameter: presynaptic firing rate, PSP size (Bremaud et al, 2007) for each presynaptic spike or number of inputs (Parker, 2003; Oswald et al, 2009) to name only a few. We do not distinguish here between these different factors. We seek to determine how these two sources of firing rate heterogeneity interact. Thus, we adapt and apply a previously developed theoretical framework (Ly, 2015) to a delayed feedforward spiking network model of the ELL electrosensory pathway. The model can qualitatively capture the different firing rate ranges depending on different stimuli, and enables an experimental prediction about how the effective network connectivity is related to intrinsic heterogeneity. Specifically, the fitted model along with our theory predicts that, when electrosensory stimuli is low frequency (a signature of same-sex interactions), target pyramidal cells that are less excitable (higher spike thresholds) have relatively stronger excitatory and inhibitory presynaptic input and cells that are more excitable (lower spike thresholds) have weaker excitatory and inhibitory presynaptic input. When the stimuli is high frequency (a signature of opposite-sex courtship), the opposite happens: target pyramidal cells that are less excitable (higher spike thresholds) have relatively weaker excitatory and inhibitory presynaptic input and cells that are more excitable (lower spike thresholds) have stronger excitatory and inhibitory presynaptic input. We further demonstrate the utility of the theory by showing how the range of firing rates from the data can be captured with a delayed feedforward network model with fixed synaptic input strengths, as opposed to changing the strengths in the prescribed way. Our work demonstrates how theoretical analysis can be used to elucidate the interactions of neural attributes with various stimuli, and specifically with presynaptic network inputs that are not fully understood in the ELL pathway (Bol et al, 2011). Given the widespread nature of feedforward pathways in the nervous system (Berman and Maler, 1999; Ferster and Miller, 2000; Bruno and Simons, 2002; Pouille and Scanziani, 2001; Bastian et al, 2004) and the generic structure and parameters in our model, we argue that our result characterizes a general mechanism applicable to a variety of systems.

2 Methods

2.1 Delayed feedforward network model

The population of interest consists of superficial pyramidal cells receiving afferent sinusoidal input and network input via the parallel fiber (often termed 'feedback' in the ELL of electric fish hindbrain even though it is really a delayed feedforward open-loop) from granule cells. We simply model the parallel fiber input with an equal number of excitatory (E) and inhibitory (I) cells that also receive afferent sinusoidal input. The granule cell input to the superficial pyramidal cells are delayed by O(10) ms to mimic the ELL pathway (Bol et al, 2011). This configuration captures the essence of parallel fiber input in steady state (Bol et al, 2011; Maler, 2007). All cells are modeled as leaky integrate-and-fire (LIF) point neurons. Note that we have chosen to exclude the specific attributes known in the ELL (e.g., bursting mechanisms, synaptic plasticity, etc.) to have a rather general feedforward network and mechanisms that do not rely on the particularities of this specific system. The general structures of such networks are common to many pathways and areas of the nervous system (visual system (Ferster and Miller, 2000), somatosensory system (Bruno and Simons, 2002), hippocampus (Pouille and Scanziani, 2001), electrosensory system (Berman and Maler, 1999; Bastian et al, 2004), etc.). The intrinsic heterogeneity and synaptic variability are modeled simply by two parameters that are allowed to vary among the neurons.
The equations for the superficial pyramidal neurons indexed by \( j \in \{1, 2, \ldots, N\} \) are:

\[
\begin{align*}
\tau_n \frac{dv_j}{dt} &= I_{aff}(t) - v_j - q_j g_i(t - \tau_{del})(v_j - \mathcal{E}_I) - q_j g_e(t - \tau_{del})(v_j - \mathcal{E}_E) + \sigma_p \eta_j(t) \\
v_j(t^*) &\geq \theta_j \text{ (refractory period)} \Rightarrow v_j(t^* + \tau_{ref}) = 0 \\
\tau_n \frac{d\eta_j}{dt} &= -\eta_j + \sqrt{\tau_n} \xi_j(t) \\
I_{aff}(t) &:= I_0 + A \sin(2\pi q t) \quad (1)
\end{align*}
\]

where the leak, inhibitory and excitatory reversal potentials are 0, \( \mathcal{E}_I \), and \( \mathcal{E}_E \), respectively with \( \mathcal{E}_I < 0 < \mathcal{E}_E \), (the voltage is scaled to be dimensionless so that a leak/resting value of -65 mV maps to 0 and a threshold voltage of -55 mV maps to 1 (the average threshold), see Table II for other parameters), and \( \xi_j(t) \) are uncorrelated (in time and across neurons) white noise processes with 0 mean and unit variance.

The afferent input \( I_{aff}(t) \) is purely sinusoidal, which is known to be a good model for the signal the electric fish is exposed to during interactions with conspecific (i.e., the so-called "beat" amplitude modulation (Maler 2007)) since afferents are linear for stimuli of realistic strength (Gussin et al 2007).

The second line in the equations describes the refractory period at spike time \( t^* \): when the neuron’s voltage crosses threshold \( \theta_j \) (intrinsic heterogeneity), the neuron goes into a refractory period for \( \tau_{ref} \) where the voltage is undefined \( \mathcal{E}_E \) after which we set the neuron’s voltage to 0.

The conductance variables \( (g_i(t - \tau_{del}) \) and \( g_e(t - \tau_{del}) \) are determined by the delayed feedforward input (equations to follow) and are both scaled by a factor \( q_j \) that is specific to the \( j \)th neuron because the inputs are disynaptic (Maler 2007). \( q_j \) introduces synaptic variability that is loosely motivated by recent results by Xue et al (2014), who found that pyramidal neurons receive relatively similar proportions of excitation and inhibition in layer 2/3 of mammalian visual cortex (i.e., some cells receive more E/I while some cells receive less E/I). This type of synaptic variability has been used in other models to study heterogeneity (Chelaru and Dragoi 2008). Note that synaptic variability can be distinct for every cell in the network (i.e., number of connections) but in our case, it does not need to be so. Here, the synaptic variability \( q_j \) represent any aspects of the network input that lead to the variability in its strength from cell to cell.

The equations for the cells modeling the delayed feedforward network inputs are similar in form but have different parameter values, and their activity determines the synaptic conductance values in the aforementioned population. This is a simple model of the granule cells that provide network inputs to the superficial pyramidal neurons in the ELL system (Maler 2009, Chacron et al 2005), see Figure II.A. There are \( 2N_f \) cells in the delayed feedforward population, with equal numbers of excitatory (\( N_f \)) and inhibitory cells, indexed by \( I \):

\[
\begin{align*}
\tau_n \frac{dv_l}{dt} &= c_l \cdot I_{aff}(t) - v_l + \sigma_p \eta_l(t) \\
v_l(t^*) &\geq 1 \text{ (refractory period)} \Rightarrow v_l(t^* + \tau_{ref}) = 0 \\
\tau_n \frac{d\eta_l}{dt} &= -\eta_l + \sqrt{\tau_n} \xi_l(t) \\
\tau_d \frac{dG_i}{dt} &= -G_i + A_l \\
\tau_r \frac{dA_l}{dt} &= -A_l + \tau_r \alpha \sum_k \delta(t - t_k) \\
g_e(t) &= s_e \sum_{\nu \in \{E \text{ cells}\}} G_{\nu}(t) \\
g_i(t) &= s_i \sum_{\nu \in \{I \text{ cells}\}} G_{\nu}(t) \quad (2)
\end{align*}
\]

1 In refractory, the other variables are governed by their ODEs
Table 1 Parameter values for delayed feedforward network

| Parameter  | Value |
|------------|-------|
| $N$        | 1,000 |
| $\tau_m$  | 10 ms |
| $\tau_{ref}$ | 1 ms |
| $\xi_I$   | -0.5  |
| $\xi_E$   | 6.5   |
| $\sigma_I$ | 0.5   |
| $\tau_{del}$ | 20 ms |
| $\tau_n$  | 5 ms  |
| $I_0$      | 0.6   |
| $A$        | 0.3   |
| $N_f$      | 200   |
| $\tau_{f_{ref}}$ | 0.5 ms |
| $\sigma_F$ | 1     |
| $\tau_d$  | 10 ms |
| $\tau_r$  | 2 ms  |
| $\alpha$  | 2     |

The parameter that scales $I_{af}(t)$: $c_l$, is 1 with excitatory neurons and $c_l = 1.2$ with inhibitory neurons; the rest of the parameter values are in Table 1 (or will vary and be specified later).

In all neuron models, the firing rate $\nu_j$ is defined by:

$$\nu_j := \frac{\text{Number of spikes}}{\text{Total time}}$$

(3)

The firing rate is a common statistical quantity of interest and is, among other spike metrics, known to have important implications for encoding signals [Kay, 1993].

Initially, the delayed feedforward network is randomly connected to the superficial pyramidal neurons with a 20% connection probability (Erdős-Rényi graph)\(^2\). In most of the figures (except where indicated), we set $s_e = 2.3/(0.2 + N_f) = 0.0575$ and $s_i = 1/(0.2 + N_f) = 0.025$.

In addition to the overwhelming evidence for both forms of heterogeneity in various cortical areas, there is evidence in our data that suggests the synaptic input mediates firing rate heterogeneity. Figure \(^3\) shows the range of firing rates ($\max_j \nu_j - \min_j \nu_j$) in the recorded ELL pyramidal cell population as a function of the frequency of the sinusoidal afferent stimuli. Note that the results in this paper are qualitatively the same when considering the standard deviation $\sigma(\nu)$ across the population (results not shown) as a measure of firing rate heterogeneity. The intact network that contains delayed feedforward network inputs from the granule cells is shown in black. This network input can be blocked or diminished so that the pyramidal cells only receive direct afferent input (see section 2.2), which has a big effect on the firing rate distribution (red). Any reasonable model should take the effect of granule cell network input into account; specifically this delayed feedforward input should result in less firing rate heterogeneity with lower frequencies than the firing rate heterogeneity observed with higher frequencies. This model and our previously developed theory [Ly, 2015] enables the structure of the synaptic variability to dramatically effect the firing rate distribution.

2.1.1 Distributions of the intrinsic heterogeneity and synaptic variability

The two parameters ($q_j, \theta_j$) are varied to give different firing rate distributions. The means of both $q$ and $\theta$ are set to 1, and the parameters $\sigma_q$ and $\sigma_{\theta}$ quantify the level of the synaptic variability and

\(^2\) To mimic the ELL, we make the connectivity from both E and I cells in the delayed feedforward population to the superficial pyramidal neurons the same, although having distinct connectivity does not qualitatively change any of the results.

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intrinsic heterogeneity, in the following way:

\[ q \sim 1 + \sigma_q \times (U - 0.5) \]  
\[ \theta \sim e^\mathcal{N} \]  

where \( U \) is the uniform distribution on \([0, 1]\), and \( \mathcal{N} \) is normal distribution with mean \(-\sigma_\theta^2/2\) and standard deviation \(\sigma_\theta\), so that \( \theta \) has a log-normal distribution with mean 1 and variance: \(e^{\sigma_\theta^2} - 1\). Throughout this paper, we set \( \sigma_\theta = 0.2 \) and \( \sigma_q = 1 \), which can give a wide distribution of firing rates.

### 2.1.2 Changing the correlation between intrinsic heterogeneity and synaptic variability

A key way to change the firing rate heterogeneity, where the overall level of heterogeneity of \(q\) and \(\theta\) are approximately the same, is by setting the correlation between \(q\) and \(\theta\) to a particular value. Given the vectors \(q\) and \(\theta\), we fix \(q\) to the same values but transform \(\theta\) so that the Pearson’s correlation coefficient is \(\rho \in (-1, 1)\) in such a way that the transformed vector has the same mean and variance as original \(\theta\). The methods used to accomplish this were previously described in the Appendix of Ly (2013).

### 2.2 Electrophysiology

Surgery was as previously described in Marsat et al. (2009); Middleton et al. (2006). *A. leptorhynchus* were anesthetized with tricaine methanesulfonate (Finquel MS222, Argent Chemical Laboratories, Redmond, WA) and respirated during surgery. The skull above the ELL was removed after local anesthetic was applied to the wound. The skull was glued to the post for stability. General anesthesia was stopped, and the fish was immobilized with an injection of curare (pancuronium bromide, Holzkirchen, Germany) and transferred to the experimental tank (40 × 45 × 20 cm) containing water kept between 25\(^\circ\)C and 27\(^\circ\)C and with conductivity around 100–400 \(\mu\)S. In vivo, single-unit recordings were performed using metal-filled extracellular electrodes (Frank and Becker, 1964). Pyramidal cells can easily be located by the anatomy of the ELL and overlying cerebellum as well as by their response properties (Maler et al., 1991; Saunders and Bastian, 1984). All experiments and protocols were approved by the Institutional Animal Care and use Committee.

Our data set includes 11 superficial pyramidal cells stimulated with a continuous AM sinewaves of 5 Hz and 27 neurons stimulated with the high frequency 120 Hz stimulus. Stimuli are applied in a spatially global configuration with a pair of electrodes positioned on opposite sides of the tank. This spatial configuration drives both the afferent inputs to the pyramidal cells but also the delayed feedforward network. The delayed feedforward input can be blocked by either injecting lidocaine in the axon bundle that innervates the caudal cerebellum. Alternatively, we can present the stimulus in a spatially local geometry that saturates – but is limited to – the receptive field of the afferent input of the cell being recorded, thereby preventing activation of the delayed feedforward network. Both methods were used with similar effects on firing rate. The details of the stimulation, recording and lidocaine block are described in Marsat and Maler (2012).

### 3 Results

We first demonstrate that a delayed feedforward spiking neural network model can capture the population firing rate features exhibited in the experimental data, with only 1 parameter change to capture two distinct types of realistic sensory stimuli. We apply our theory for firing rate heterogeneity to the fitted model to determine the relationship of the heterogeneous parameters that captures the firing rate heterogeneity in the data. Finally, we demonstrate the utility of the theory for effective network connectivity with example networks where the probability of connection is structured in such a way to obtain the prescribed correlation between the (heterogeneous) neural attributes derived from the analysis.
Afferent Stimuli

Superficial Pyramidal Cells

Granule Cells

Both Excitatory and Inhibitory Inputs

Fig. 1 Setup and motivation for this study. A) The generic delayed feedforward network model motivated by the ELL of weakly electric fish. The neurons of interest are the superficial pyramidal cells (equation (1)) receiving direct sinusoidal afferent input and network inputs from granule cells which also receive afferent inputs. The granule cell network inputs are delayed by $\tau_{\text{del}}$ and provide both excitatory and inhibitory inputs. B) Experimental data showing the range of firing rates ($\max_j \nu_j - \min_j \nu_j$, see equation (3)) of superficial pyramidal cells in the ELL with 2 sinusoidal afferent inputs: low and high frequency. In black is the intact network with network input from granule cells, and in red is the altered network where granule cell network input is blocked/diminished. This provides experimental evidence that the network input consisting of both excitatory and inhibitory inputs, significantly alters the firing rate distribution.

3.1 Adapting the theory for the delayed feedforward network model

Previously, analysis of a heterogeneous recurrent LIF networks provided insights to how the firing rate distribution changed as the relationship between threshold heterogeneity and synaptic variability changed (Ly, 2015). In the weakly electricfish electrosensory system, the neural network containing the superficial pyramidal neurons in the ELL is a delayed feedforward network. Fortunately, despite the different types of network, the previously developed theory for recurrent networks can be adapted to these networks (see Appendix A). In this delayed feedforward network, the resulting PDF equations have less dimensions than a recurrent network when making similar assumptions. The goal of the analysis here (and in Ly (2015)) is not to accurately capture the exact firing rates but rather to highlight a proof of principle for how the relationship between heterogeneous attributes changes the relative firing rate ranges.

In this system, there is a long history of using LIF neural networks to capture salient experimental results and in using computation/analysis to uncover details of electrosensory processing (Doiron et al, 2003; Noonan et al, 2003; Bol et al, 2011; Litwin-Kumar et al, 2012; Mejias et al, 2013). Given these previous results, it is not surprising that our network model was able to capture the population firing rate in time and for two distinct types of stimuli (see Fig. 2B, D). We sought to capture the population firing rate of both sets of experimental data (low and high frequency) by changing only one variable, the frequency of the afferent sinusoidal input: $\phi$ (see equations (1)–(2)); this allows a fair comparison of the network features for each stimuli. Moreover, the two frequencies of the sinusoidal input were obtained directly from the experiments where the afferents were driven at 5 Hz and 120 Hz, respectively. For simplicity, we do not consider the other differences in the afferent signal with these two types of stimuli (i.e., the size of the amplitude and the amplitude modulation of $I_{\text{aff}}(t)$).

The population firing rate in time is shown for low frequency in figure 2A. The model, which has noise (trial to trial variability) and the two forms of quenched variability (intrinsic and synaptic mediated by granule cell model activity), is able to capture the population average response with 2 distinct afferent stimuli (also see Fig. 2D). Here, the quenched distributions for the threshold heterogeneity $\theta$ and synaptic variability $q$ were chosen independently with $g = 0$ (see equations (4)–(5) and Methods for parameter values). We did not use an optimization routine based on particular algorithms and did not make specific choices about parameters ranges and other parameter attributes, rather we manually varied the noise levels $\sigma_{P/F}$ and afferent input parameters $I_{0}, A$ to qualitatively match the data. Since the purpose of our computational modeling is to illustrate a principle of network dynamics (specifically effective network connectivity and its relationship with intrinsic excitability/threshold), our results hold equally well with other sets of parameters we used in these same class of models.
Fig. 2 Population firing rates of the data and the delayed feedforward model match. For a fixed parameter set (see Methods and Table 1), the delayed feedforward model (B and D) captures the population firing rate from the electrophysiology (A and C) very well, and for both low and high frequencies. The two frequencies of the afferent stimuli (not shown) in the experiments are 5 Hz and 120 Hz, which are the same two values used in the model (see $\phi$ in $I_{af}(t)$ in equations (1)–(2)) and is the only difference in the model (B and D). The insets in both B and D show the models in cyan to aid visual comparisons. We set $\rho(\theta, q) = 0$ (see Methods).

The two population of presynaptic (granule) cells are relatively simple homogeneous LIF models, with firing rates that depend on the details of the afferent input $c_{I_{af}}(t)$. When $\phi = 5$ Hz, the time-averaged firing rates are $\langle r_E(t) \rangle_t = 17.1$ Hz and $\langle r_I(t) \rangle_t = 24.5$ Hz; when $\phi = 120$ Hz, $\langle r_E(t) \rangle_t = 15.8$ Hz and $\langle r_I(t) \rangle_t = 22.5$ Hz.

In Ly (2015), the relative change in firing rate range (as a function of correlation of heterogeneous attributes) in recurrent networks was captured in two different limits: (i) the asynchronous limit where the net input currents are weak (or balanced), (ii) the rhythmic limit were the net input currents are strong (see Fig. 3A, red and blue, respectively). Thus, to apply the theory in Ly (2015) to this model, we have to determine which of the two limits in the analysis is applicable to our fitted model. The simulations indicate that the regime with strong overall net current applies (i.e, 'rhythmic'). Indeed, figure 3A shows that the distance to threshold for our fitted model is small (black and green) when compared to the Recurrent, Asynchronous (red) and Recurrent, Rhythmic (blue) networks from Ly (2015). Most importantly, we are justified in choosing the network limit with strong current inputs since during the experiments the network is strongly driven by a sinusoidal stimulus. In Appendix A
The theory developed for the rhythmic regime in the recurrent network is applicable to the ELL delayed feedforward network. A) Histograms of the average (in time) distance to a neuron’s spike threshold $\theta_j$ show that the delayed feedforward networks (equation 1–2) with low (5 Hz, black) and high (120 Hz, green) frequencies is closer to the recurrent rhythmic network (blue, 800 E-cells) than the recurrent asynchronous one (red, 800 E-cells). The details of the recurrent networks and parameters are described in Ly (2015). Colored dots indicate average across the population of neurons. B) The range (max minus min) of firing rates as the correlation between $q$ and $\theta$ vary for rhythmic recurrent (and thus the delayed feedforward) networks. On the vertical axis, we set $x = (\bar{g}_E \varepsilon_E + \bar{g}_I \varepsilon_I)$ (see Appendix A for asymptotic calculation and further details). C) Simulations of the range of firing rates in the delayed feedforward networks as the correlation between $q$ and $\theta$ vary with low and high frequency sinusoidal input (same parameters as in Fig. 2). D) Similar to (C), except the sinusoidal drive is weaker with $I_0 = 0.3$ (see equation 1); this is merely to demonstrate that the theory in (B) is more accurate (see main text for why).

In the analysis, we focus on a specific limit of the reduced firing rate equations rather than dealing with a multidimensional partial differential equation. When adapted to this delayed feedforward network, the resulting reduced equations are more comprehensible with less state space dimensions. Figure 3B demonstrates how the firing rate range changes as the correlation $g$ between threshold heterogeneity and synaptic variability vary. When $g < 0$, larger $\theta_j$ tend to occur with smaller $q_j$, so the maximum of $q/\theta$ is amplified (big times big) and the minimum is diminished (small times small), resulting in a relatively
large range. When \( q > 0 \), larger \( \theta_j \) tend to occur with larger \( q_j \), so both the maximum and minimum of \( q/\theta \) are closer in value (small times big minus big times small), resulting in a relatively small range.

Since the experimental data suggests that the delayed feedforward input is crucial for observing less firing rate heterogeneity with lower frequencies than with higher frequencies (Fig. 1B), our model is satisfying in that the structure of this delayed feedforward input strongly affects the range of firing rates. Indeed, the theory applied to these parameters (Fig. 3B) is validated in the large spiking network model (Fig. 3C). Here, the range of the firing rates is plotted while \( \varphi(\theta, q) \) is varied while keeping the mean and variance (among the \( N \) pyramidal cells) fixed. There are two curves because two different sinusoidal frequencies \( \omega \) were used: 5 Hz in black and 120 Hz in green. We remark that the statistics of the granule cell input remain the same throughout the various correlation values \( \rho(\theta, q) \), but since there is (colored) noise \( \sigma_F \eta_t \), there are minor deviations for each simulated network due to finite simulation time.

The qualitative match between the theory (Fig. 3B) and the fitted model (Fig. 3C) is not perfect, and was better for a generic recurrent LIF network (Ly, 2013). The reason for this is that the parameters that fit the model violate an assumption in the calculation (Appendix A). The approximation for \( \left\langle \int_{-\infty}^{\infty} I_{aff}(t) \rho(v, \eta, t) \, dt \right\rangle \) (equation 20) where the time average is applied to each factor in the integrand, is not as good when \( I_{aff}(t) \) is stronger because the PDF \( \rho(v, \eta, t) \) is strongly coupled to the values of \( I_{aff}(t) \). Indeed, when the afferent sinusoidal input is made weaker in figure 3D where \( I_0 = 0.3 \) instead of \( I_0 = 0.6 \) (the value in Fig. 3C), the PDF \( \rho(v, \eta, t) \) is not as strongly coupled to the values of \( I_{aff}(t) \). Therefore, the qualitative match of the firing range there (Fig. 3D) to the analytic reduction (Fig. 3B) is much better than the fitted model in figure 3C.

3.2 Model prediction: strength of effective delayed feedforward inputs depends on stimuli

A natural model prediction from these modeling results (Fig. 3C) is that the effective delayed feedforward input strength is structured in a stimulus-dependent manner. With lower frequency afferent inputs, the model predicts that the pyramidal cells with higher thresholds (intrinsically less excitable) receive overall stronger delayed feedforward excitatory and inhibitory input than cells with lower thresholds (more excitable); that is, \( q > 0 \). With higher frequency afferent inputs, the model predicts that pyramidal cells with higher threshold (intrinsically less excitable) receive overall weaker delayed feedforward excitatory and inhibitory input than cells with lower thresholds (\( q < 0 \)).

Figure 4A-B shows a schematic picture of the model prediction for two pyramidal cells with lower and higher thresholds receiving inputs from 4 granule cells with all possible feedforward connections. The thickness of the arrows indicate how strong the effective network input \( q \) is from both presynaptic E and I cells. This model prediction is a statistical statement about the aggregate population and not about individual cells. For example, the theory certainly allows for cells with higher thresholds to have larger effective network inputs with high frequency inputs (appearing to violate \( q < 0 \)), but the correlation being negative (in this case) means these cases will happen less often than the other case.

Figure 4C shows the range of firing rates from the experimental data (as a function of the dominant sinusoidal frequency), compared with the fitted model where we see different firing rate ranges depending on \( q \). With the low frequency, we plot the firing rate range with the 'best' corresponding \( q \) that is closest to the firing rate range from the data (\( q = 0.2 \), recall the black curve in Fig. 3C) in cyan. With the high frequency, again we plot the firing rate range with the 'best' corresponding \( q \), which is \( q = -0.7 \) (green curve in Fig. 3C) in cyan. Given the good match between model and data, the application of the theory clearly demonstrates both how significant \( \varphi \) is in controlling the firing rate range, and the specific structure of network input strength. The difference in firing rate range cannot be attributed to the sinusoidal frequency \( \omega \) in this model because we have already seen that the firing rate range does not vary much (Fig. 3C).
Fig. 4 Model prediction about the effective network input strength (granule cells), depending on the afferent stimuli to capture the different ranges in firing rates. 

A) Cartoon of a small sub network to illustrate how intrinsic threshold $\theta$ of 2 (superficial pyramidal) neurons is related to effective network input strength $q$ that consists of both excitatory and inhibitory inputs. For low frequencies, $\rho(\theta, q) > 0$ so that neurons with smaller $\theta$ tend to have smaller effective network input $q$ (and vice-versa). 

B) With high frequencies, $\rho(\theta, q) < 0$ so that neurons with smaller $\theta$ tend to have larger effective network input $q$ (and vice-versa). 

C) The range of firing rates in the experimental recordings (black dots) are captured by the model (cyan dots). In the data, with a low frequency (5 Hz) stimuli, there were 11 neurons with trial averaged firing rates ranging from 5.8 Hz to 28.9 Hz (population average of 18.1 Hz); with a high frequency (120 Hz), there were 27 neurons with trial averaged firing rates ranging from 3.1 Hz to 76.5 Hz (population average of 11.4 Hz). In the model, the same parameters as in Fig. 2 were used, but now the correlation $\rho$ is allowed to vary. For the low frequency, $\rho = 0.2$ gives the best approximation to the range of firing rates to the data among the $\rho$ mesh values considered (see black curve in Fig. 3C), with a population average of 14.4 Hz. For the high frequency, $\rho = -0.7$ gives the best range approximation to the range of firing rates to the data (see green curve in Fig. 3C), with a population average of 11.5 Hz.
3.3 Linking theory to neural architecture to account for data

Previously we showed a direct application of the theory where the parameters ($\theta_j, q_j$) were manipulated in the computational model, resulting in firing rate ranges captured by our reduced description. In this section, we apply the theory in a different way and link it with the architecture of a neural network. A motivating reason for this is that the weakly electric fish encounters both low and high frequency stimuli in its natural environment, and it is conceivable that it may need to process both low and high frequency stimuli in rapid succession. Thus, the effective network input strength $q$ may not be able to change fast enough, which would seemingly weaken our theory. We present a network framework to overcome this issue.

The neural network model we consider here has fixed heterogeneity values ($\theta, q$) for the target pyramidal cells, and we set $\phi(\theta, q) = 0$ (although we will see this is not necessary). The network is designed so that the effective correlation between $\theta$ and $q$ are as before (i.e., $q > 0$ for smaller $\phi$ and $q < 0$ for larger $\phi$). Networks in the previous sections have a 20% connection probability, so some cells do not receive network inputs; by effective we mean that pyramidal cells that are actually connected the delayed feedforward have this $q$. Here, only a subset of presynaptic granule cells will be activated and respond (i.e., spike) to sinusoidal input (previously they all responded equally), and different groups of these granule cells will respond depending on the sinusoidal frequency $\phi$ (see Fig. 5A and Appendix B for details). Indeed, there is evidence for frequency tuning of granule cells in the ELL (Bol et al., 2011). By construction, pyramidal cells are differentially activated by delayed feedforward input, but note that as before, all pyramidal cells receive the same afferent sinusoidal input $I_{aff}$. The connectivity rules for the delayed feedforward network will no longer be random (Erdős-Rényi graph, see Figure 6B) but rather the activated presynaptic cells have a higher probability of connecting to pyramidal cells that result in the desired $q$; figure 5A shows a cartoon schematic of this idea. In implementing this idea, we make the assumption that the effective $\phi(\theta, q)$ varies continuously from a high (positive) value to low (negative) value as $\phi$ increases. There are numerous ways to effectively have various $q$ values in the pyramidal cells, and we only present 2 instances of the network (see Appendix B for connectivity rules and other details). Figure 5B illustrates the connectivity rules for Network 1: the activated presynaptic cells at a low frequency have a higher probability of connection to the red cells on a diagonal band in $(q, \theta)$ space (color bar represents actual number of inputs with various $\phi$). The reason for this diagonal band with positive slope is that the effective $q$ will be positive. As $\phi$ increases, other sets of presynaptic cells are activated and the probability of connection is again higher for target cells that are in the red band. Figure 5C illustrates the connectivity rules for Network 2 that are similar to the previous network except the region is different. The activated presynaptic cells at a low frequency have a higher probability of connection to the red cells that form two triangular wedges in $(q, \theta)$ space. Again, as $\phi$ increases, other sets of presynaptic cells are activated and the probability of connection is higher for cells that are in the red band.

In these two networks (Network 1, 2), there are overall less presynaptic cells activated than before (we kept the same $N_j = 200$ and $N = 1000$), so we scale the strength of the conductances ($s_c, s_s$) so that the firing rates are comparable to the previous model. With a fixed architecture, afferent sinusoidal input is provided to all populations as before and only the frequency $\phi$ is varied (with selective activation of presynaptic granule cells). The resulting firing rate ranges (Fig. 5D) are clearly well described by our reduced analytic descriptions. Specifically, the effective correlation $\phi$, which in this case was attributed to a particular frequency $\phi$, is the determining factor in the firing rate range. Figure 5E shows this directly; the firing rate ranges from these two networks are plotted as a function of effective correlation (reverse scale on x-axis) and again the range is larger with $\phi < 0$ than $\phi > 0$. Unlike the previous neural network, we were able to obtain different firing rate ranges with the same fixed $(\theta, q)$ and fixed connectivity (with structure, it is not completely random).

---

3 In Fig. 5E, the effective correlation for a given $\phi$ is the Pearson’s correlation calculated on the set of $(\theta_j, q_j)$ weighted by the number of presynaptic inputs.
Fig. 5 Using the theory to capture the firing rates ranges in the data with fixed \((\theta, q)\), with \(\rho(\theta, q) = 0\). A) Demonstrates how the theory can be used to get different firing rates ranges. Depending on frequency on the afferent stimulus, selective activation of granule cells can provide effectively more presynaptic input to the desired set of pyramidal cells that have a specific \(g(\theta, q)\) (i.e., \(g > 0\) for low frequencies and \(g < 0\) for higher frequencies). B) Network 1: a particular network architecture that captures the desired \(g\), for fixed \((\theta, q)\), shown for three different frequencies. The coloring indicates a measure of the effective input (red is more, blue is less): (number of presynaptic inputs from granule cells) \(\times\) (Probability granule cell fires), scaled to have values in \([0,1]\). C) Network 2: another network architecture that captures the desired \(g\). In both networks, we assume \(g\) varies continuously as the frequency increases; this assumption is not necessary and is only made to demonstrate the utility of the theory. D) Comparing how the firing rate ranges vary with frequency in both network models and in the experimental data. Consistent with the theory, we see the range generally increases with frequency. In both network models, since the total numbers of granule and pyramidal cells are kept fixed (see Table 1), the conductance values here are slightly larger than in the previous figures: \(s_e = 0.0375\), \(s_i = 0.06\) (see equations 1–2). E) The range of firing rates as a function of the effective \(g\) (reverse scale, positive is left, negative is right) from the two networks is consistent with the theoretical analysis.
We have adapted and applied a theory for firing rate heterogeneity to a generic delayed feedforward network, and used data from the electrosensory system of the weakly electric fish to constrain the model. The data suggests that firing rate heterogeneity is larger for higher frequency sinusoidal input (agonizing signal with same sex animals) than with lower frequency sinusoidal input (courtship of opposite sex), and that this difference in heterogeneity is operated by the delayed feedforward. With our theory and computational models, in order to account for the observed firing rate statistics, we predict that the effective network connectivity is dynamically modulated depending on stimulus features. Our work uses theoretical analysis to specifically predict how the interactions of neural attributes (threshold heterogeneity and synaptic strengths) lead to heterogeneous firing rate statistics with various stimuli.

Other cellular or network features certainly effect the firing rate heterogeneity, but we focus on threshold heterogeneity because threshold is known to be important in this system (Middleton et al, 2009), and other cellular attributes can be related to the threshold in the leaky integrate-and-fire model (Mejías and Longtin, 2012, 2014). Besides the previously mentioned reasons for the existence and importance of different synaptic strengths, our data indicate that delayed feedforward input activity from the specific network of granule cells significantly effects the firing rate distribution. Several other attributes of sensory neurons and and the distribution of their heterogeneity will influence the way they encode information (tuning, non-linearity, plasticity, to name only a few); investigating how network dynamic influences these heterogeneities is a rich research direction for future studies.

Although the fitted model was best described by the ‘rhythmic’ regime where the presynaptic inputs were large, the theory in Ly (2015) also accounts for asynchronous regimes where the presynaptic inputs are weaker and background fluctuations significantly effects spiking. In those regimes, the relationship between the heterogeneous attributes lead to different firing rate ranges than the ‘rhythmic’ regimes. Thus, the experimental predictions can be reexamined and potentially augmented if other fitted models happen to operate in a different regime. An alternative explanation for the modulation of firing rate heterogeneity is that the heterogeneity of the presynaptic firing rate could modulate with stimulus (in our models the presynaptic firing rates are statistically homogeneous) and the superficial pyramidal cells would inherit this heterogeneity. However, this would not explain all the experimental data: with the afferent input strength being identical in all cases, blocking the delayed feedforward input increased the firing rate heterogeneity for low frequencies (and decreased it for high frequencies). Clearly, the delayed feedforward input cannot simply contribute to the cells’ firing rate heterogeneity, otherwise blocking the feedback would systematically reduce heterogeneity by removing a source of variability. Instead, our model shows that firing rate heterogeneity can either increase or decrease simply but varying the correlation between network input strength and the cells’ excitability (threshold). Experimental verification that this mechanism does indeed play a role in the ELL would require a thorough set of experiments, probably involving both in-vitro and in-vivo recording. We know that this mechanism is not the only one affecting firing rate heterogeneity in the ELL. For example, a previous study showed that the delayed feedforward input interacts with the burst-generating mechanism to produced stereotyped responses (less heterogeneous) during low-frequency stimulation (Marsat and Maler, 2012). This study can in fact fit the theory presented here. If one considers bursting as a source of intrinsic excitability, that paper showed strong positive network input interacts with this intrinsic excitability, the implication being that a positive correlation between the two would lead to strong stereotyped bursts (low heterogeneity). Clearly, ELL pyramidal cells have many more properties than are being explicitly modeled here, but it is precisely the reason that makes our theory so general and applicable to a wide variety of systems.

We focus specifically on firing rate heterogeneity because it is the first order statistic and crucial in understanding the mechanisms that lead to efficient coding. The effects of heterogeneity of neural attributes on coding and dynamics of neural networks is important and has been studied by numerous authors both in a general theoretical framework (Hermann and Touboul, 2012; Mejías and Longtin, 2012; Hunsberger et al, 2014; Mejías and Longtin, 2014) and in specific neural systems (Shamir and Sompolinsky, 2006; Chelaru and Dragoi, 2008; Marsat and Maler, 2010; Marsat et al, 2012). Our results differ from
these studies in many ways, but largely because i) we account for two heterogeneous attributes, ii) we make a specific prediction about synaptic strengths depending on the target (pyramidal) cells and stimulus features. The results here may be applicable to other systems given how common feedforward pathways are and how well spiking neuron models can capture the statistics of neural network activity.

Firing rate heterogeneity is just one statistical measure of the network response, and there are other measures that may also be crucial in the context of neural coding. The spike coherence of the response with the afferent stimuli is commonly used in the electrosensory system (Chacron et al., 2005; Mehaffey et al., 2008; Middleton et al., 2009), and thus an important future direction is how the heterogeneity of the firing rate in time effects the efficiency of coding. In addition to the afferent sinusoidal input, communication signals in electric fish also consist of brief chirps. However, the predominant electrical signal in time is the nearly sinusoidal input that we have considered. The afferent sinusoidal activity without the transient chirp at the very least sets the stage for the neural network to readily decode the chirp input, and is thus an important component (Marsat and Male, 2012). Another potentially important measure is the second order statistics, or the spike count correlation, of the pyramidal cells (Averbeck et al., 2006; Cohen and Kohn, 2011; Doiron et al., 2016). Theoretical analyses of such measures when focusing on heterogeneity are complicated (Josić et al., 2009; Ecker et al., 2011; Ly et al., 2012) and beyond the scope of this current paper.

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Appendix A: Asymptotic calculation for the relative range of firing rate distribution

The asymptotic calculations were all based on an expression for the firing rate of an individual neuron via the PDF or Population Density framework that has been commonly used in spiking models in cortex models (Knight, 1972; Wilbur and Rinzel, 1982; Fourcaud and Brunel, 2002; Brunel and Latham, 2003; Tranchina, 2003) and other areas (Barna et al., 1995; Brown et al., 2003; Huertas and Smith, 2006). In addition to the firing rate, this framework has been useful in calculating many statistical quantities of the spike train (Brunel et al., 2001; Richardson, 2007, 2008) and to study the stability of coupled networks (Knight, 1972; Abbott and van Vreeswijk, 1993; Brunel and Hakim, 1999; Gerstner, 2000; Ly and Ermentrout, 2010). It can also be employed as a time saving computational tool (Nykamp and Tranchina, 2000; Omurtag et al., 2000; Apfaltrer et al., 2006; Ly and Tranchina, 2007). We focus on the range of firing rates and use the framework to gain analytic insight into the dynamics.

To employ the framework and for feasibility, we make some technical assumptions:

(i) the (average) population firing rate is a good approximation to the presynaptic input rate with random connectivity
(ii) a single p.d.f. function is adequate to describe a single population’s activity
(iii) the heterogeneity is driven by \((q_j, \theta_j)\) only

The complexities that arise in a recurrent network (nonlinear PDF equation) never came about (Ly, 2015) in our specific analysis because of the networks here are delayed feedforward networks. Moreover, the resulting PDF equations have lower dimensions than a recurrent network. We begin by writing down the probability density function for both (E and I) presynaptic populations that provide delayed feedforward input.

\[
\rho^E(v, \eta, t) \, dv \, d\eta = \Pr (\text{presyn E cell} \in \{(v, v + dv) \cap (\eta, \eta + d\eta)\})
\]

\[
\rho^I(v, \eta, t) \, dv \, d\eta = \Pr (\text{presyn I cell} \in \{(v, v + dv) \cap (\eta, \eta + d\eta)\})
\]
The PDF equations for the presynaptic E population are:

\[
\frac{\partial \rho^E}{\partial t} = -\frac{\partial}{\partial v} \{J_V(v, \eta, t)\} - \frac{\partial}{\partial \eta} \{J_\eta(v, \eta, t)\}
\]

\[
J_V(v, \eta, t) = \frac{1}{\tau_m} [I_{af}(t) - v + \sigma \eta \rho^E]
\]

\[
J_\eta(v, \eta, t) = \frac{1}{\tau_n} [-\eta \rho^E - \frac{1}{2} \frac{\partial \rho^E}{\partial \eta}]
\]

\[
J_V(1, \eta, t) = J_V(0, \eta, t + \tau_{ref})
\]

\[
r^E(t) = \int_{-\infty}^{\infty} J_V(1, \eta, t) d\eta
\]

where \(r^E(t)\) is the population firing rate. The presynaptic I population is the same except for the factor of 1.2 that scales \(I_{af}(t)\):

\[
\frac{\partial \rho^I}{\partial t} = -\frac{\partial}{\partial v} \{J_V(v, \eta, t)\} - \frac{\partial}{\partial \eta} \{J_\eta(v, \eta, t)\}
\]

\[
J_V(v, \eta, t) = \frac{1}{\tau_m} [(1.2)I_{af}(t) - v + \sigma \eta \rho^I]
\]

\[
J_\eta(v, \eta, t) = \frac{1}{\tau_n} [-\eta \rho^I - \frac{1}{2} \frac{\partial \rho^I}{\partial \eta}]
\]

\[
J_V(1, \eta, t) = J_V(0, \eta, t + \tau_{ref})
\]

\[
r^I(t) = \int_{-\infty}^{\infty} J_V(1, \eta, t) d\eta
\]

For simplicity, we assume the synaptic conductances of the target (superficial pyramidal) cells can be averaged in time (see equation (2)):

\[
g_e(t) = s_e \int r^E(t - t')K(t') dt'
\]

\[
g_i(t) = s_i \int r^I(t - t')K(t') dt'
\]

where \(K\) is the alpha function kernel:

\[
K(t) = H(t) \alpha \tau_r \left[ e^{-t/\tau_r} - e^{-t/\tau_d} \right]
\]

and \(H(t)\) is the Heaviside step function and \(\tau_r < \tau_d\) (a common assumption in models of synapses). This kernel is unconventional in that \(\int_{-\infty}^{\infty} K(t) dt = \alpha \tau_r \) and not 1.

Finally, the PDF for the target cells:

\[
\rho(v, \eta, t) dv d\eta = Pr (\text{pyramidal cell } \in \{(v, v + dv) \cap (\eta, \eta + d\eta)\})
\]

are described by:

\[
\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial v} \{J_V(v, \eta, t)\} - \frac{\partial}{\partial \eta} \{J_\eta(v, \eta, t)\}
\]

\[
J_V(v, \eta, t) = \frac{1}{\tau_m} [I_{af}(t) - v - q_j g_e(t - \tau_{del})(v - \mathcal{E}_E) - q_j g_i(t - \tau_{del})(v - \mathcal{E}_I) + \sigma \eta \rho] \rho
\]

\[
J_\eta(v, \eta, t) = \frac{1}{\tau_n} [-\eta \rho - \frac{1}{2} \frac{\partial \rho}{\partial \eta}]
\]

\[
J_V(1, \eta, t) = J_V(0, \eta, t + \tau_{ref})
\]

\[
r_j(t) = \int_{-\infty}^{\infty} J_V(\theta_j, \eta, t) d\eta
\]
The firing rate \( r_j(t) \) is not a population firing rate, but rather the firing rate of the \( j^{th} \) neuron in the population. We implicitly assume that the only difference between cells is given by the two heterogeneous parameters: \((\theta_j, q_j)\).

Our goal is not to capture the time-varying firing rates (which are still difficult even with these assumptions because of the three coupled PDEs that each have 2 spatial dimensions and time), but rather we are interested in the time-averaged firing rates. This enables a compact expression for how the heterogeneity \((\theta, q)\) relationship controls the range of steady-state firing rates. We have:

\[
\nu_j := \langle r_j(t) \rangle_t
\]

We approximate

\[
\int_{-\infty}^{\infty} I_{aff}(t) \rho(v, \eta, t) \, dt \approx \int_{-\infty}^{\infty} I_{aff}(t) \xi \langle \rho(v, \eta, t) \rangle_t \, d\eta,
\]

and similarly for the expressions with \( g_c/e \). This leads to:

\[
\nu_j \approx \frac{1}{\tau_m} \left[ I_0 - \theta_j + g_E (E_{E} - \theta_j) - g_I (\theta_j - E_I) \right] \frac{f(\theta_j)}{\tau_m} + \frac{\sigma_p \rho(\theta_j, \eta)}{\tau_m} \int_{-\infty}^{\infty} \eta \, d\eta
\]

where \( f(v) = \int \rho(v, \eta) \, d\eta \) is the steady-state marginal voltage distribution (equal to the time-average, assuming ergodic theorems apply), and \( g_E = \alpha E_c (r^E(t)), g_I = \alpha E_I (r^I(t)) \). One could simply numerically simulate these equations, but there is not much analytic insight gained in understanding how \((\theta, q)\) and \( g(\theta, q) \) alter the firing rate range. In applying dimension reduction methods, there are issues that arise in trying to accurately capture the firing rate \cite{Ly}. Thus, we apply a simple (quantitatively inaccurate) dimension reduction method where we assume \( \eta \) is frozen and average over the resulting firing rate \cite{Moreno}. We also ignore the effects of the refractory period \( \tau_{ref} \). The firing rate is then simply:

\[
\nu_j(\theta_j, q_j) \approx \int_{-\infty}^{\infty} \nu_{det}(\theta_j, q_j; \eta) \frac{e^{-\eta^2}}{\sqrt{\pi}} \, d\eta
\]

\[
\nu_{det}(\theta_j, q_j; \eta) = \begin{cases} 0, & \text{if } \frac{2g_E(\theta_j, q_j; \eta)}{g_E(\theta_j, q_j; \eta) + \sigma_p \rho + I_0} \leq \theta_j \\ \frac{1 + q_j g_E(\theta_j, q_j; \eta) + \sigma_p \rho + I_0}{1 + q_j g_E(\theta_j, q_j; \eta) + \sigma_p \rho + I_0}, & \text{if } \frac{2g_E(\theta_j, q_j; \eta)}{g_E(\theta_j, q_j; \eta) + \sigma_p \rho + I_0} > \theta_j \end{cases}
\]

The parameters \((\theta_j, q_j)\) determine how one \( \nu_j \) differs from another; to see how the combined effects of threshold heterogeneity and synaptic variability alter \( \nu_j \), we consider a specific limit. That is, the simulations indicate that the the net conductance are large in the fitted model (Fig. 5A), thus, we consider the large firing rate limit of the term in the integrand \( \nu_{det} \), to get:

\[
\tau_m \nu_{det}(\theta_j, q_j) = \frac{1 + q_j (g_E + g_I)}{\log \left( \frac{q_j (g_E + g_I) + \sigma_p \rho + I_0 - \theta_j (1 + q_j (g_E + g_I))}{q_j (g_E + g_I) + \sigma_p \rho + I_0} \right)}
\]

\[
= \frac{q_j (g_E + g_I)}{\theta_j} + \frac{\sigma_p \rho + I_0}{\theta_j} - \frac{1}{2} (1 + q_j (g_E + g_I))
\]

\[
- \frac{12q_j (g_E + g_I) + \sigma_p \rho + I_0 - \theta_j (1 + q_j (g_E + g_I))}{(1 + q_j (g_E + g_I))^2 \theta_j}
\]

\[
+ O \left( z^2 (1 + q_j (g_E + g_I)) \right)
\]

\[
\text{where } z := \theta_j \frac{1 + q_j (g_E + g_I)}{q_j (g_E + g_I) + \sigma_p \rho + I_0 - \theta_j (1 + q_j (g_E + g_I))}
\]

\[
\text{Although ignoring the refractory period could be problematic for large firing rates, we emphasize that the purpose of our this analysis is not for quantitative matching but rather for an analytic explanation. A similar calculation with the refractory period was performed (not shown) but the results were not insightful.}
\]
This calculation is very similar to the one in [Ly, 2015]. The key term is the first term in equation (25),

\[
\frac{q_j}{\theta_j}(\hat{g}_E E_E + \hat{g}_I E_I)
\]

which is the dominant term assuming \(\nu_{det}\) is large. Substituting the expansion (25) into the integral approximation (22) only changes terms with \(\eta\) in them (i.e., the dominant term does not change and the term \(\sigma_p \eta/\theta_j\) evaluates to 0). This shows analytically that the term \(q_j/\theta_j\) is the dominant source of firing rate heterogeneity, and that we can approximate:

\[
\max_j \nu_j - \min_j \nu_j \approx C \left[ \max_j \frac{q_j}{\theta_j} - \min_j \frac{q_j}{\theta_j} \right]
\]

(27)

Appendix B: Details of network connectivity and model in section 3.3

We used two networks, which we generically labeled as Network 1 and Network 2 (see Fig. 5), to help demonstrate the utility of the theory for firing rate ranges with different architectures than random (Erdös-Rényi graph). We first describe how we selectively activate the granule cells that provide delayed feedforward input to the pyramidal cells, and then describe the connectivity rules for each network.

Selective activation of granule cells. Instead of providing constant sinusoidal drive to each of the \(2N_f\) presynaptic granule cells, the afferent stimuli \(I_{aff}(t) = I_0 + A \sin(2\pi \phi t)\) is scaled by a parameter \(C(l, \phi)\):

\[
I_{aff}(t) = C(l, \phi) \left[ I_0 + A \sin(2\pi \phi t) \right]
\]

that depends on both frequency \(\phi\) and the index of cell \(l \in \{1, 2, \ldots, N_f\}\) (\(2N_f\) total because there are both excitatory and inhibitory presynaptic cells). The afferent stimuli to the target pyramidal cells is the same as before (see equation (1)). Before providing the formula for \(C(l, \phi)\), we note that the strength of the sinusoidal drive will follow a (scaled) beta distribution where the location of the maximum value increases as \(\phi\) increases. We use:

\[
C(l, \phi) = 1.5 \frac{x(l)^{19} (1 - x(l))^{21.52 \times \frac{125}{125} - 21}}{\max_{1 \leq l \leq N_f} \beta(l, \phi)}
\]

(28)

where

\[
\beta(l, \phi) = x(l)^{19} (1 - x(l))^{21.52 \times \frac{125}{125} - 21}
\]

\[
x(l) = \frac{2.5 \text{ Hz}}{125 \text{ Hz}} \left( \lfloor l/4 \rfloor - 1/2 \right)
\]

The term \(\beta(l, \phi)\) is simply the numerator of the fraction in \(C(l, \phi)\) so that \(C(l, \phi) \in (0, 1.5)\). The variable \(x(l)\) is the end result of mapping the \(l^{th}\) presynaptic neuron to one of 50 frequencies (equally spaced by 2.5 Hz from 1.25 Hz to 123.75 Hz) and normalizing by 125 Hz. Here we are assuming \(\phi \in [0, 125]\) Hz so that \(x(l) \in (0, 1)\); other frequencies can easily be incorporated with minor adjustments to the above formulas. Finally, notice that in \(x(l)\), we have the term: \(\lfloor l/4 \rfloor\), which denotes rounding up after dividing by 4; this essentially groups presynaptic neurons into groups of size 4 that receive the same sinusoidal drive. Figure 6A illustrates how the sinusoidal drive to the presynaptic cells, indexed by \(l\), vary with several fixed frequencies \(\phi\).

Connectivity rules for Network 1. To illustrate the usefulness of the theory, we implemented a static delayed feedforward network with fixed \((\theta, q)\) and certain connectivity rules (see below). The presynaptic granule cells are indexed as before via \(l\), and the target pyramidal cells by \(j\). Recall that both \(E\) and \(I\) cells in the presynaptic population have the same connectivity for simplicity.

Each pyramidal cell \(j\) has an associated \((\theta_j, q_j)\) (Fig. 5B,C), and since each presynaptic \(l\) cell’s sinusoidal drive depends on frequency, the probability of connection is specified so that the effective
Fig. 6 Activation of presynaptic cells depends on the frequency of the afferent sinusoidal input. A) The strength of the sinusoidal input $C(l, \phi)$ (see equation (28)) for particular frequencies; from left to right, $\phi = 3.75, 33.75, 63.75, 93.75, 123.75$ Hz. B) Showing the number of presynaptic connections (out of $N_f = 200$) for each of the $N = 1000$ target pyramidal cells (sorted from smallest to largest) in both networks. Notice the structure of the connectivity, compared to completely random connectivity (black dash line, with 20% connection probability).

$\phi(\theta, q)$ results in firing rate heterogeneity consistent with the data (i.e., $\phi > 0$ for low frequencies and $\phi < 0$ for high frequencies). The connection probability is closely related to Figure 5B: that is:

Low frequencies activate a subset of presynaptic cells, the probability that those presynaptic cells are connected to target cells with $(\theta_j, q_j)$ in a region that gives $\phi > 0$ is high (Fig 5B, red); the probability is lower with the other target cells (blue). Similar connection probability rules apply for high frequencies. In both networks we considered, the connectivity scheme assumes that as the afferent sinusoidal frequency increases, $\phi$ decreases monotonically. Again, this is a questionable assumption that we have made only to provide a proof of principle for how our theory can be used. In Network 1, different effective $\phi$ values are obtained by lines with slopes proportional to $\phi$. Of course, there are an infinite number of ways to arrive at a desired $\phi$ value. The probability of a connection is:

$$P(l \text{ is connected to } j) = e^{-100d(l,j)}$$

where

$$d(l,j) = \min_{(\theta_0,q_0) \in \mathbb{B}(l)} \sqrt{(\theta_j - \theta_0)^2 + (q_j - q_0)^2}$$

$$\mathbb{B}(l) = \{(\theta,q) | m_l(q - \bar{q}) - 0.1 < \theta - \bar{\theta} < m_l(q - \bar{q}) + 0.1\}$$

$$m_l = (1 - 2x(l)) \frac{\max \theta_j - \min \theta_j}{\max q_j - \min q_j}; \quad \bar{q} = \frac{1}{2} \left( \max q_j + \min q_j \right); \quad \bar{\theta} = \frac{1}{2} \left( \max \theta_j + \min \theta_j \right);$$

$x(l) \in (0, 1)$ was defined above (i.e., scaled frequency that drives $l$ well). The function $d(l,j)$ is the Euclidean distance in $(\theta, q)$ space to the band $\mathbb{B}(l)$, which consists of $(\theta, q)$ values that give the desired $\phi$. Note that the slope of the band $m_l$ goes from positive to negative as $l$ increases.

Connectivity rules for Network 2. The rules in this network are similar in spirit to Network 1 but the region that gives an effective $\phi$ value is no longer rectangular but rather a wedge (compare Fig. 5B).
The probability of a connection is:

\[ P(l \text{ is connected to } j) = e^{-100d(l,j)} \]

where \( d(l,j) = \min_{(\theta_0,q_0) \in \mathcal{W}(l)} \sqrt{(\theta_j - \theta_0)^2 + (q_j - q_0)^2} \)

\[ \mathcal{W}(l) = \mathcal{W}_1(l) \cup \mathcal{W}_2(l) \]
\[ \mathcal{W}_1(l) = \left\{ (\theta, q) \middle| (n_l - 0.4)(q - \bar{q}) < \theta - \bar{\theta} < (n_l + 0.4)(q - \bar{q}) \right\} \]
\[ \mathcal{W}_2(l) = \left\{ (\theta, q) \middle| (n_l + 0.4)(q - \bar{q}) < \theta - \bar{\theta} < (n_l - 0.4)(q - \bar{q}) \right\} \]

\[ n_l = (0.8 - 1.6x(l)) \frac{\max_j \theta_j - \min_j \theta_j}{\max_j q_j - \min_j q_j}; \quad \bar{q} = \frac{1}{2} \left( \max_j q_j + \min_j q_j \right); \quad \bar{\theta} = \frac{1}{2} \left( \max_j \theta_j + \min_j \theta_j \right); \]

\( x(l) \in (0,1) \) has the same definition as before, but the function \( d(l,j) \) is now the Euclidean distance in \((\theta,q)\) space to the region \( \mathcal{W}(l) \) which are 2 triangular wedges (Fig. 5C).

The resulting number of connections for both Network 1, 2 are not random but rather has structure (Fig. 5B).

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