Differential contributions of synaptic and intrinsic inhibitory currents to speech segmentation via flexible phase-locking in neural oscillators

Benjamin R. Pittman-Polletta[1*], Yangyang Wang[2], David A. Stanley[1], Charles E. Schroeder[3], Miles A. Whittington[4], Nancy J. Kopell[1],

1 Department of Mathematics & Statistics, Boston University, Boston, MA **2** Department of Mathematics, University of Iowa, Iowa City, IA **3** Translational Neuroscience Division, Center for Biomedical Imaging and Neuromodulation, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA **4** Hull York Medical School, York, UK

* benpolletta@gmail.com

Abstract

Current hypotheses suggest that speech segmentation – the initial division and grouping of the speech stream into candidate phrases, syllables, and phonemes for further linguistic processing – is executed by a hierarchy of oscillators in auditory cortex. Theta (∼3-12 Hz) rhythms play a key role by phase-locking to recurring acoustic features marking syllable boundaries. Reliable synchronization to quasi-rhythmic inputs, whose variable frequency can dip below cortical theta frequencies (down to ∼1 Hz), requires "flexible" theta oscillators whose underlying neuronal mechanisms remain unknown. Using biophysical computational models, we found that the flexibility of phase-locking in neural oscillators depended on the types of hyperpolarizing currents that paced them. Simulated cortical theta oscillators flexibly phase-locked to slow inputs when these inputs caused both (i) spiking and (ii) the subsequent buildup of outward current sufficient to delay further spiking until the next input. The greatest flexibility in phase-locking arose from a synergistic interaction between intrinsic currents that was not replicated by synaptic currents at similar timescales. Our results suggest that synaptic and intrinsic inhibition contribute to frequency-restricted and -flexible

phase-locking in neural oscillators, respectively. Their differential deployment may enable neural oscillators to play diverse roles, from reliable internal clocking to adaptive segmentation of quasi-regular sensory inputs like speech.

Author summary

Oscillatory activity in auditory cortex is believed to play an important role in auditory and speech processing. One suggested function of these rhythms is to divide the speech stream into candidate phonemes, syllables, words, and phrases, to be matched with learned linguistic templates. This requires brain rhythms to flexibly phase-lock to regular acoustic features of the speech stream. How neuronal circuits implement this task remains unknown. In this study, we explored the contribution of inhibitory currents to flexible phase-locking in neuronal theta oscillators, believed to perform initial syllabic segmentation. We found that a combination of specific intrinsic inhibitory currents at multiple timescales, present in a large class of cortical neurons, enabled exceptionally flexible phase-locking, suggesting that the cells exhibiting these currents are a key component in the brain's auditory and speech processing architecture.

1 Introduction

Conventional models of speech processing [1–3] suggest that decoding proceeds by matching chunks of speech of different durations with stored linguistic memory patterns or templates. Recent oscillation-based models have postulated that this template-matching is facilitated by a preliminary segmentation step [4–6], which determines candidate speech segments for template matching, in the process tracking speech speed and allowing the adjustment (within limits) of sampling and segmentation rates [7, 8]. Segmentation plays a key role in explaining a range of counterintuitive psychophysical data that challenge conventional models of speech perception [6, 9–11], and conceptual hypotheses [4, 5, 12–16] suggest cortical rhythms entrain to regular acoustic features of the speech stream [17–20] to effect this preliminary grouping of auditory input.

Speech is a multiscale phenomenon, but both the amplitude modulation of

continuous speech and the motor physiology of the speech apparatus are dominated by syllabic timescales – i.e., δ/θ frequencies ($\sim$1-9 Hz) [21–25]. This syllabic timescale information is critical for speech comprehension [9, 10, 24, 26–29], as is speech-brain entrainment at δ/θ frequencies [30–36], which may play a causal role in speech perception [37–40]. Cortical θ rhythms – especially prominent in the spontaneous activity of primate auditory cortex [41] – seem to perform an essential function in syllable segmentation [9–11, 35], and seminal phenomenological [9] and computational [42–45] models have proposed a framework in which putative syllables segmented by θ oscillators drive speech sampling and encoding by γ ($\sim$30-60 Hz) oscillatory circuits. The fact that oscillator-based syllable boundary detection performs better than classical algorithms [43, 44] argues for the role of endogenous rhythmicity – as opposed to merely event-related responses to rhythmic inputs – in speech segmentation and perception.

However, there are issues with existing models. *In vitro* results show that the dynamics of cortical, as opposed to hippocampal [46], θ oscillators depend on intrinsic currents at least as much as (and arguably more than) synaptic currents [47, 48]. Yet existing models of oscillatory syllable segmentation assume θ rhythms are paced by synaptic inhibition [43, 45], and employ methodologies – integrate-and-fire neurons [43] or one-dimensional oscillators [45] – incapable of capturing the dynamics of intrinsic currents. This is important because the variability of syllable lengths between syllables, speakers, and languages, as well as across linguistic contexts, demands "flexibility" – the ability to phase-lock, cycle-by-cycle, to quasi-rhythmic inputs with a broad range of instantaneous frequencies [4, 10], including those below its intrinsic frequency – of any cortical θ oscillator tasked with syllabic segmentation. In contrast to this functional constraint, (synaptic) inhibition-based rhythms have been shown to exhibit *inflexibility* in phase-locking, especially to input frequencies lower than their intrinsic frequency [49, 50]. Furthermore, the pattern of spiking exhibited by a flexible θ rhythm – which we show depends markedly on the intrinsic currents it exhibits – has important implications for downstream speech processing, being hypothesized to determine how and at what speed β- ($\sim$15-30 Hz) and γ-rhythmic cortical circuits sample and predict acoustic information [45, 51]. And while much is known about phase-locking in neural oscillators [52–56], the existing literature sheds little light on these issues: few studies

have examined the physiologically relevant "strong forcing regime", in which input pulses are strong enough to elicit spiking [57]; little work has explored how oscillator parameters influence phase-locking to inputs much slower or faster than an oscillator's intrinsic frequency [58]; and few published studies explore oscillators exhibiting intrinsic outward currents on multiple timescales [59].

In addition, the lack of reliable acoustic markers of syllable boundaries, and the higher information density of the consonantal clusters that mark *linguistic* syllable boundaries relative to the high energy and long-duration vowels at their center, has led to the suggestion that reliable speech-brain entrainment may reverse the syllabic convention, relying on the high energy vocalic nuclei at the center of each syllable to mark segmental boundaries [4, 10, 14, 43, 60], enabling both robust determination of these boundaries and dependable sampling of the consonantal evidence that informs segment identity. These reversed "theta-syllables" are hypothesized to be the candidate cortical segments distinguished and passed downstream for further processing [14] by auditory cortical θ rhythms, but whether θ rhythms differentially entrain to different speech channels (associated with the acoustics of consonants and vowels) remains unexamined.

Motivated by these issues, we explored whether and how the biophysical mechanisms giving rise to cortical θ oscillations affect their ability to flexibly phase-lock to inputs containing frequencies slower than their intrinsic frequency. We tested the phase-locking capabilities of biophysical computational models of neural θ oscillators, parameterized to spike intrinsically at 7 Hz, and containing all feasible combinations of: (i) θ-timescale subthreshold oscillations (STOs) resulting from an intrinsic θ-timescale hyperpolarizing current (as observed in θ-rhythmic layer 5 pyramids [48, 61], and whose presence is denoted by "M" in the name of the model); (ii) an intrinsic "super-slow" (δ-timescale) hyperpolarizing current (also observed *in vitro* [48], and present in models with an "S"); and (iii) θ-timescale synaptic inhibition, as previously modeled [43] (present in models with an "I"). We drove these oscillators with synthetic periodic and quasi-periodic inputs, as well as speech inputs derived from the TIMIT corpus [62].

In all three cases, models exhibiting the combination of STOs and super-slow rhythms observed *in vitro* (models MS and MIS) showed markedly more flexible phase-locking than primarily inhibition-paced models (models I, MI, and IS). Exploring the activation of these three inhibitory currents immediately prior to spiking revealed

that this extremely flexible phase-locking was driven by a novel complex interaction between θ-timescale STOs and super-slow K currents. This interaction enabled a buildup of outward (inhibitory) current during input pulses, sufficiently long-lasting to silence spiking during the period between successive inputs, even when this period lasted for many θ cycles, that was absent from oscillators paced by synaptic inhibition. This difference between inhibition-based models and models paced by STOs and the super-slow K current was especially pronounced for speech inputs, where intrinsic outward currents led to stronger phase-locking to the mid-vocalic channels of sample sentences, supporting the notion that θ-rhythmic syllable segmentation may make use of θ-syllables rather than conventional, linguistically defined ones.

2 Results

2.1 Modeling cortical θ oscillators

To investigate the dependence of frequency flexibility in phase-locking on the biophysics and dynamics of inhibitory currents, we employed Hodgkin-Huxley type computational models of cortical θ oscillators. In these models, θ rhythmicity was paced by either or both of two mechanisms: synaptic inhibition with a fast rise time and a slow decay time as in the hippocampus [46] and previous models of syllable segmentation [43]; and θ-frequency sub-threshold oscillations (STOs) resulting from the interaction of a pair of intrinsic currents activated at subthreshold membrane potentials – a depolarizing persistent sodium current and a hyperpolarizing and slowly activating m-current [47] (Fig. 1, 2B). A super-slow potassium current introduced a δ timescale into the dynamics of some models (Fig. 1, 2C) and helped to recreate dynamics observed *in vitro* [48]. Thus, in addition to spiking and leak currents, our models included up to three types of outward – i.e. hyperpolarizing and thus spike suppressing, and here termed inhibitory – currents: an m-current or slow potassium current (I_{m}) with a voltage-dependent time constant of activation of ∼10-45 ms; recurrent synaptic inhibition (I_{inh}) with a decay time of 60 ms; and a super-slow K current ($I_{\mathrm{K_{SS}}}$) with (calcium-dependent) rise and decay times of ∼100 and ∼500 ms, respectively. The presence of these three hyperpolarizing currents was varied over six models – M, I, MI, MS, IS, and MIS –

whose names indicate the presence of each current: M for the m-current, I for synaptic inhibition, and S for the super-slow K current (Fig. 1).

We began by qualitatively matching *in vitro* recordings from layer 5 θ-resonant pyramidal cells [48] (Fig. 2D). As their resting membrane potential is raised over a few mV, these RS cells exhibit a characteristic transition from tonic δ-rhythmic spiking to tonic θ-rhythmic spiking through so-called mixed-mode oscillations (MMOs, here doublets of spikes spaced a θ period apart occurring at a δ frequency) [48]. *In vitro* data suggests that this pattern of spiking is independent of recurrent synaptic inhibition, arising instead from intrinsic inhibitory currents. To replicate this behavior, we constructed a Hodgkin-Huxley neuron model paced by both I_{m} and $I_{\mathrm{K_{SS}}}$ (Fig. 1, model MS, & Fig. 2A). While *in vitro*, these layer 5 θ-rhythmic pyramidal cells receive δ-rhythmic EPSPs, this rhythmic excitation is not required in our model, which exhibited MMOs in response to tonic input (Fig. 2D).

We then constructed five additional models based on model MS (Fig. 1). To compare the performance of this model to inhibition-based oscillators, we obtained model IS by replacing I_{m} with feedback synaptic inhibition I_{inh} from a SOM-like interneuron (Fig. 1, model IS, schematic), adjusting the leak current and the conductance of synaptic inhibition to get a frequency-current (FI) curve having a rheobase and inflection point similar to that of model MS (Fig. 1, model IS, FI curve). In the remaining models, only the leak current conductance was changed, to enable 7 Hz tonic spiking at roughly similar values of I_{app}; except for the presence of the three inhibitory currents, all other conductances were identical to those in models MS and IS (see Table 3). Two models without $I_{\mathrm{K_{SS}}}$ (model M and model I) were constructed to explore this current's contribution to model phase-locking. Two more models were constructed with both I_{m} and I_{inh} to explore the interactions of these currents. (Models with neither I_{m} nor I_{inh} lacked robust 7 Hz spiking.) For all simulations, we chose and fixed I_{app} so that all models exhibited intrinsic rhythmicity at the same frequency, 7 Hz (Fig. 1, inset FI curves, red circles), allowing us to directly compare the frequency range of phase-locking between models.

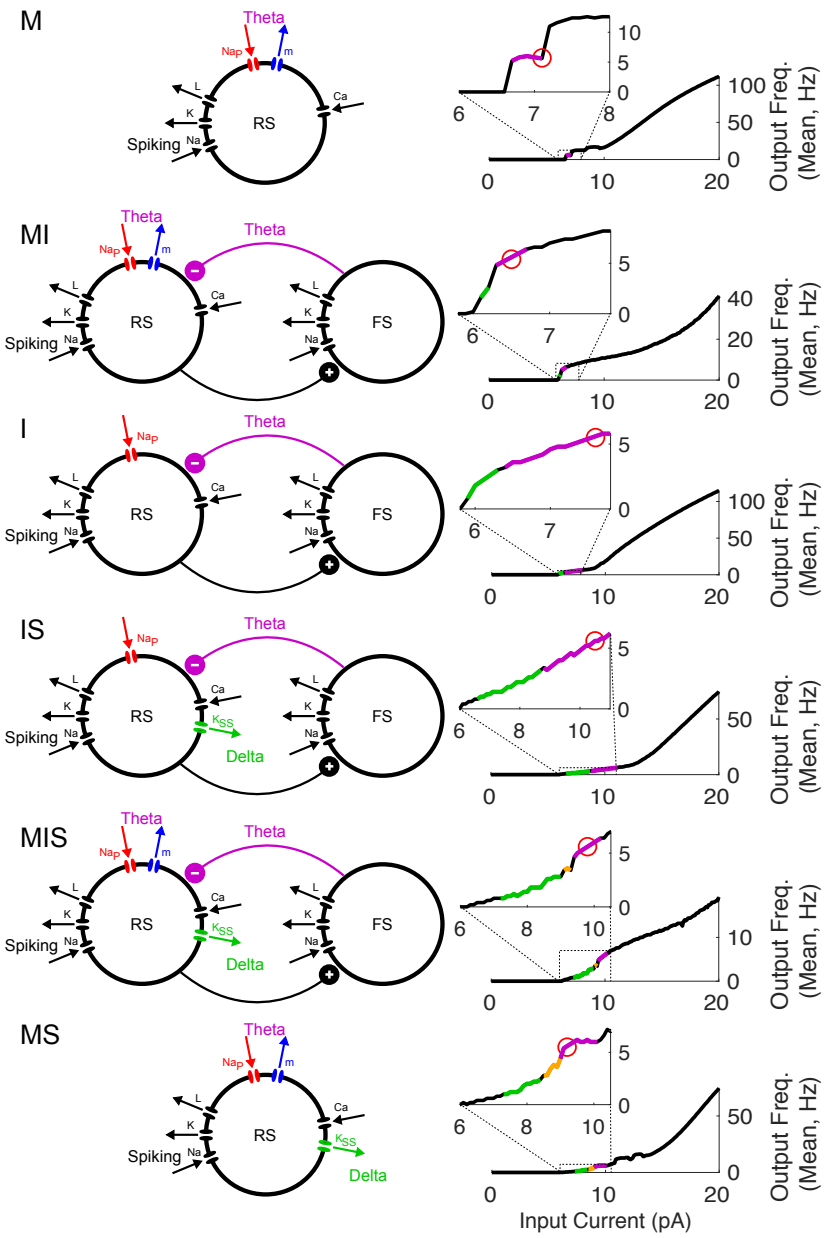

Fig 1. Model θ oscillators. Schematics (left) show the currents present in each model, color-coded according to timescale of inhibition (δ in green, θ in purple). FI curves (right) show the transition of spiking rhythmicity through δ and θ frequencies as I_{app} increases (δ in green, θ in purple, and MMOs in gold); the red circle indicates the point on the FI curve at which I_{app} was fixed, to give a 7 Hz firing rate.

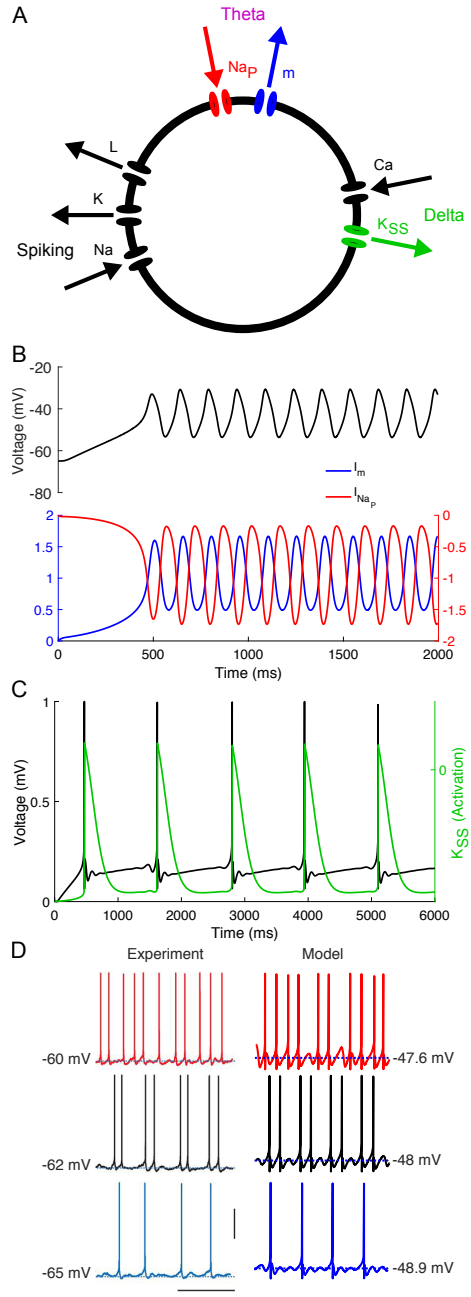

Fig 2. Model MS reproduces *in vitro* data. (A) Diagram of model MS. Arrows indicate directions of currents (i.e., inward or outward). (B) θ timescale STOs arise from interactions between m- and persistent sodium currents in a model without spiking or Ca-dependent currents (only g_{m} and g_{Na_P} nonzero). (C) δ timescale activity-dependent hyperpolarization arises from a super-slow K current. (D) Comparison between *in vitro* (adapted from [48]) and model data (calibration: 50 μV, 0.5 ms).

2.2 Phase-locking under strong forcing

We tested the entrainment of these model oscillators using a variety of synthetic and speech inputs, all strong enough to cause spiking with each input "pulse".

2.2.1 Rhythmic inputs

To begin mapping the frequency rage of phase-locking in our models, we measured model phase-locking in response to regular rhythmic inputs, modeled as smoothed square-wave current injections to the RS cells of all three models. The frequencies of these inputs ranged from 0.25 to 23 Hz, and their duty cycles were held constant at 1/4 of the input period (see Methods), to mimic the bursts of excitation produced by deep intrinsic bursting (IB) cells projecting to deep regular spiking (RS) cells [48]. For inputs at all frequencies, the total (integrated) input over 30 s was normalized, and multiplied by a gain varied from 0 to 4. Entrainment was measured as the phase-locking value (PLV) of RS cell spiking to the input rhythm phase (see Section 4.3).

The results of these simulations are shown in Fig. 3, with models ordered by increasing frequency flexibility of phase-locking, as measured by the lower frequency limit of appreciable phase-locking. The most flexible model (MS) was able to phase lock to input frequencies as low as 1.5 Hz even when input strength was relatively low, while the least flexible model (M) was unable to phase-lock to input frequencies below 7 Hz. For high enough input strength, all models were able to phase-lock adequately to inputs faster than 7 Hz, up to and including the fastest frequency we tested (23 Hz). However, much of this phase-locking occurred with less than one spike per input cycle (see white contours, Fig. 3). Notably, models MI and MIS exhibited one-to-one phase-locking to periodic inputs at input strengths twice as high as other models. Simulations showed that this was due to a higher overall level of inhibition, as the range of input strengths over which one-to-one phase-locking was observed increased with the conductances of both the m- and synaptic currents (Fig. S1).

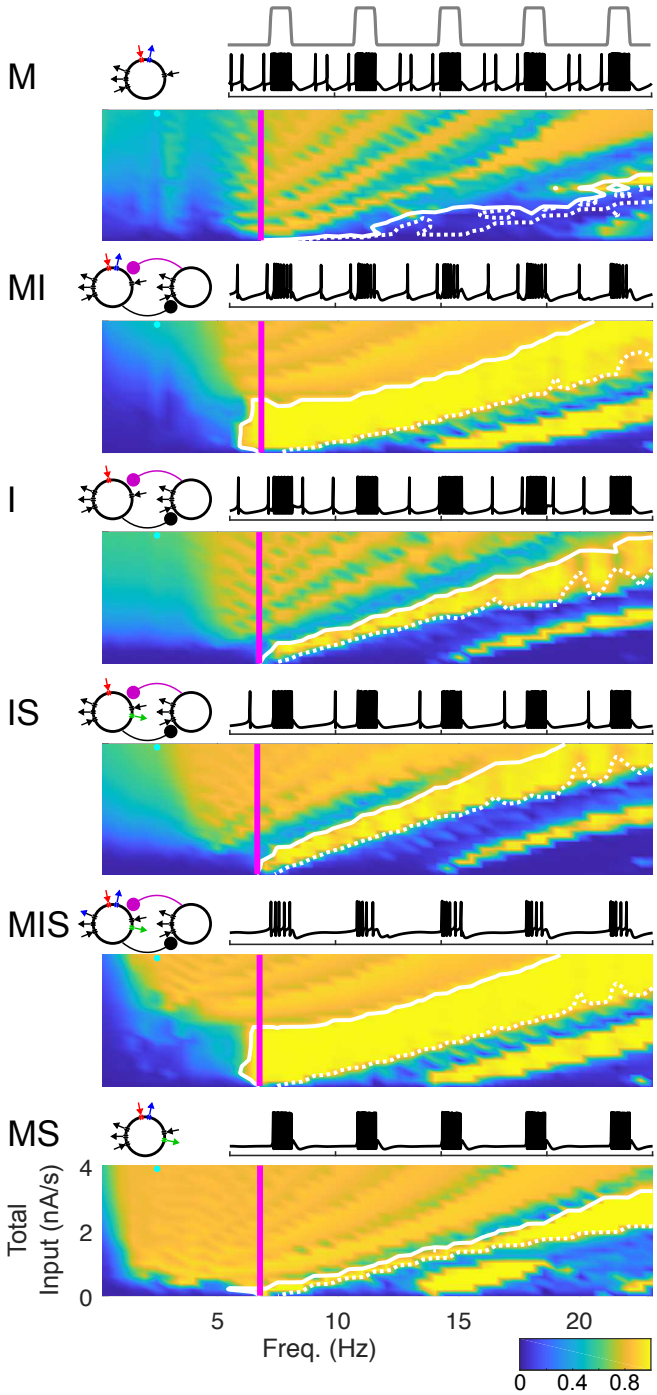

Fig 3. Phase-Locking as a Function of Periodic Input Frequency & Strength. False-color images show the (spike-rate adjusted) phase-locking value (PLV, see Section 4.3) of spiking to input waveform. Vertical magenta lines indicating intrinsic spiking frequency. Solid white contour indicates boundary of phase-locking with one spike per cycle; dotted white contour indicates boundary of phase-locking with 0.9 spikes per cycle. Bands in false-color images of PLV are related to the number of spikes generated per input cycle: the highest PLV occurs when an oscillator produces one spike per input cycle, and PLV decreases slightly (from band to band) as both the strength of the input and the number of spikes per input cycle increases. Schematics of each model appear above and to the left; sample traces of each model appear above and to the right (voltage traces in black, input profile in gray, two seconds shown, input frequency 2.5 Hz, total input −3.4 nA/s, as indicated by cyan dot on the false-color image). Total input per second was calculated by integrating input over the entire simulation.

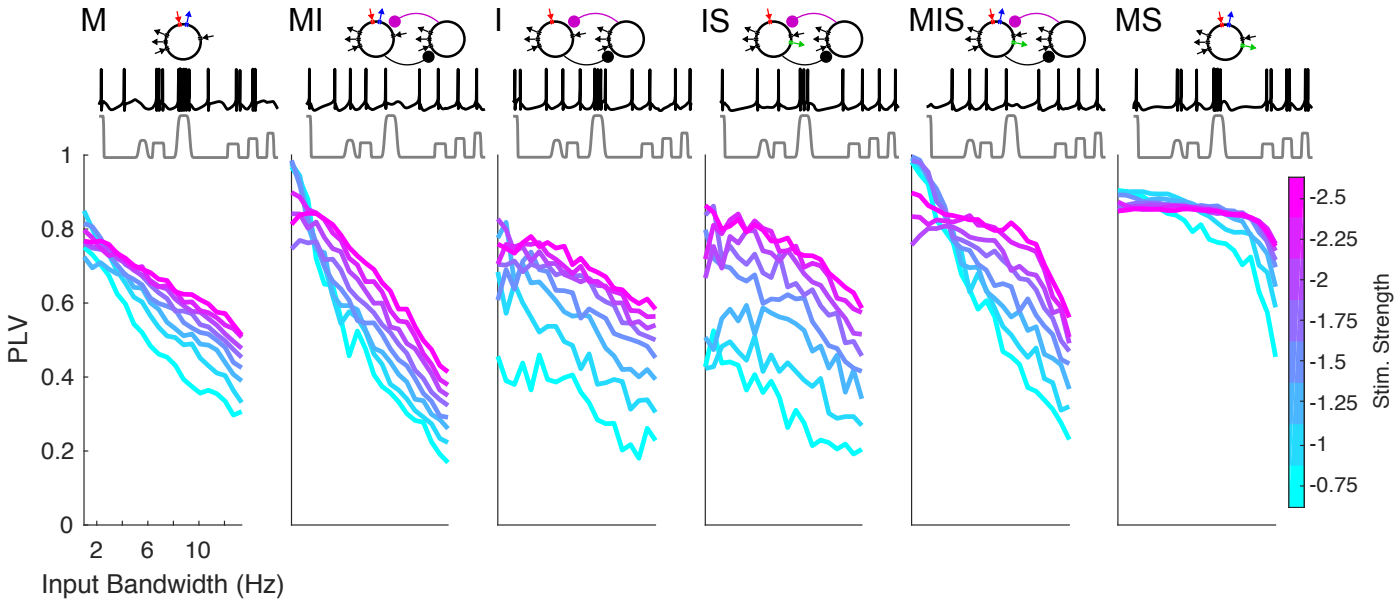

Fig 4. Phase-Locking to Quasi-Rhythmic Inputs. Plots show the (spike-rate adjusted) phase-locking value of spiking to input waveform, for inputs of varying input strength as well as varying bandwidth and regularity (see Methods & Table 5). All inputs have a center frequency of 7 Hz. Schematics of each model appear above. Sample traces from each model are shown in black, in response to inputs shown in gray, having a bandwidth of 10.65 Hz and an input gain of 1.1; 1.1 second total is shown.

2.2.2 Quasi-rhythmic inputs

Next, we tested whether the frequency selectivity of phase-locking exhibited for periodic inputs would carry over to quasi-rhythmic inputs, by exploring the phase-locking behavior of model θ oscillators in response to trains of input pulses in which pulse duration, interpulse duration, and pulse waveform varied from pulse to pulse. The latter were chosen (uniformly) randomly from ranges of pulse "frequencies", "duty cycles", pulse shape parameters, and onset times (see Methods, Equation 3). To create a gradient of sets of (random) inputs with different degrees of regularity, we systematically varied the intervals from which input parameters were chosen (Table 5); we use "bandwidth" here as a shorthand for this multi-dimensional gradient in input regularity. Input pulse trains with a "bandwidth" of 1 Hz were designed to be similar to the 7 Hz periodic pulse trains from Section 2.2.1.

For these "narrowband", highly regular inputs, all six models showed a high degree of phase-locking (Fig. 4). In contrast, phase-locking to "broadband" inputs was high only for the models that exhibited broader frequency ranges of phase-locking to regular

rhythmic inputs. At high input strengths, model MS in particular showed a high level of phase-locking that was nearly independent of input regularity (Fig. 4). Notably, model MIS mirrored the ability of model MS to phase-lock to broadband inputs at high input intensity, while showing frequency selective phase-locking at low input intensity. Indeed, model MIS phase-locked to weak, narrowband quasi-rhythmic inputs better than any other model, perhaps due to its large region of one-to-one phase-locking (Fig. 4).

2.2.3 Speech inputs

Finally, we tested whether frequency flexibility in response to rhythmic and quasi-rhythmic inputs would translate to an advantage in phase-locking to real speech inputs selected from the TIMIT corpus [62]. We also tested how phase-locking to the speech amplitude envelope might differ between auditory frequency bands, examining the response of each model to 16 different auditory channels, ranging in center frequency from 0.1 to 3.2 kHz, extracted from 20 different sentences selected blindly from the TIMIT corpus by a model of the cochlea and subcortical nuclei responsible for auditory processing [63]. We varied the input strength of these speech stimuli with a multiplicative gain that varied between 0 and 2, and averaged the PLV of RS cell spiking to auditory channel phase over the 20 sample sentences (Fig. 5, Section 4.3).

All models exhibited the strongest phase-locking to the mid-vocalic channels ($\sim$0.2-0.81 kHz), with peak phase-locking to the 0.32 kHz channel. For these channels, the strength of phase-locking for each model was consistent with the models' ability to phase-lock flexibly to periodic and varied pulse inputs. Raster plots of model responses to 8 sample channels of a single sample sentence (Fig. 5, right) showed that the phase-locking of model MS was characterized in part by a *lack* of spiking when there was *no* speech input; the importance of this spiking delay to flexible phase-locking is discussed further in the next section (2.3.1).

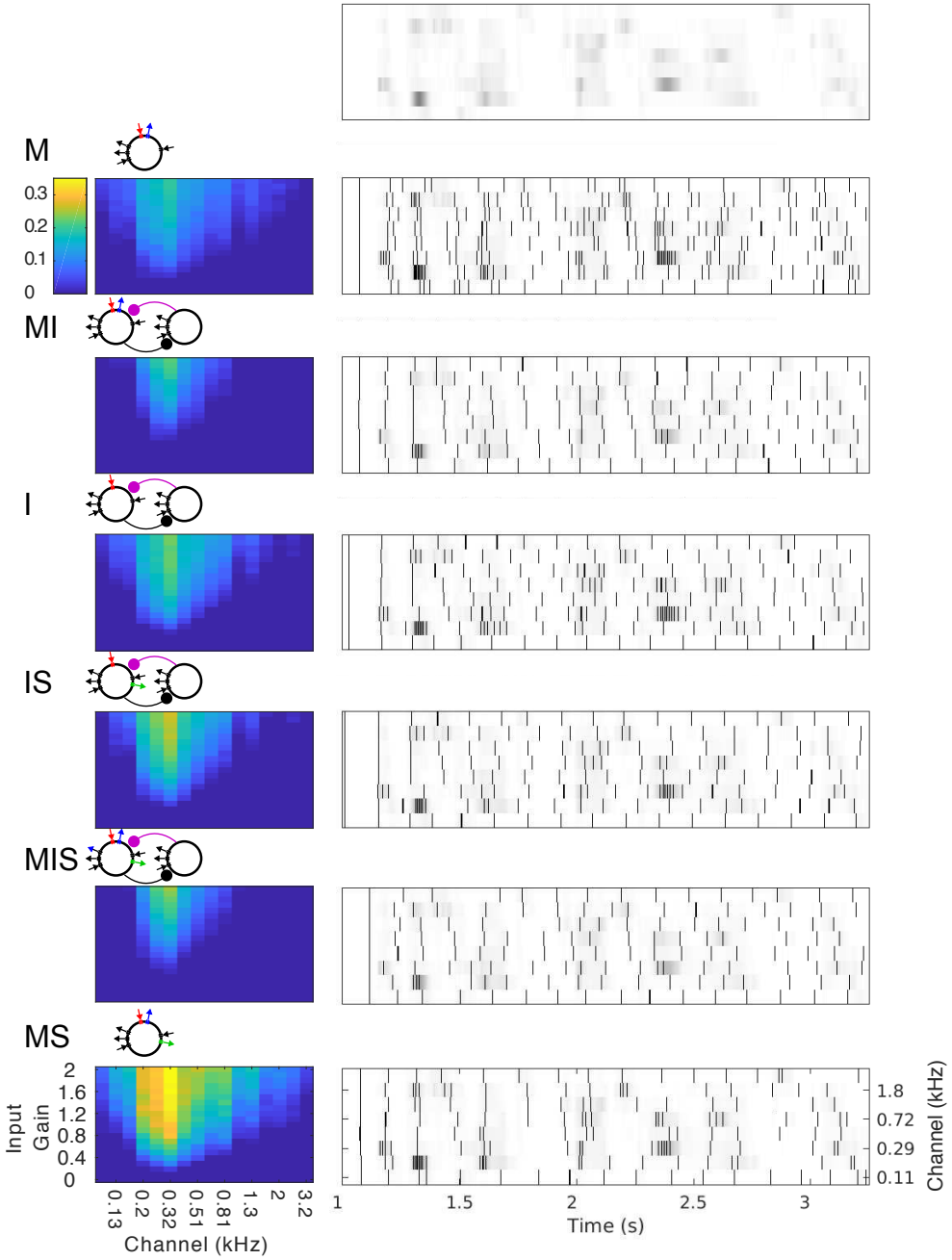

Fig 5. Phase-Locking to Speech Inputs. False-color plots (left) show the (spike-rate adjusted) PLV of spiking to speech input waveforms, for different auditory channels (x-axis) as well as varying input strengths (y-axis, see Methods). Gray-scale plots (right) show the spiking response of each model to a selection of 8 auditory channels for a single example sentence. The amplitude of each auditory channel is shown in gray-scale; the top plot shows these amplitudes without any model response. The spiking in response to each channel is overlaid as a raster plot, with a black vertical bar indicating each spike. Schematics of each model appear to the upper left.

2.3 Mechanisms of phase-locking

2.3.1 Role of post-input spiking delay

Given that both the most selective and the most flexible oscillator were paced by the m-current, we sought to understand how the dynamics of outward currents contributed to the observed gradient from selective to flexible phase-locking. We hypothesized that phase-locking to input pulse trains in our models depended on the duration of the delay until the next spontaneous spike following a single input pulse. Our rationale was that each input pulse leads to a burst of spiking, which in turn activates the outward currents that pace the models' intrinsic rhythmicity. These inhibitory currents hyperpolarize the models, causing the cessation of spiking for at least a θ period, and in some cases much longer. If the pause in spiking is sufficiently long to delay further spiking until the next input arrives, phase-locking is achieved, given that the next input pulse will also cause spiking (as a consequence of being in the strong forcing regime). In other words, if D is the delay (in s) between the onset of the input pulse and the first post-input spike, then the lower frequency limit f^* of phase-locking satisfies

$$1/f^* \leq D \Longrightarrow f^* \geq 1/D. \tag{1}$$

To test this hypothesis, we measured the delay of model spiking in response to single spike-triggered input pulses, identical to single pulses from the periodic inputs discussed in Section 2.2.1, with durations corresponding to periodic input frequencies of 7 Hz or less, and varied input strengths. The fact that these pulses were triggered by spontaneous rhythmic spiking allowed a comparison between intrinsic spiking and spiking delay post-input (Fig. 6, left), which showed a correspondence between flexible phase-locking and the duration of spiking delay. We also used spiking delay and Eq. 1 to estimate the regions of phase-locking for each model oscillator. In agreement with our hypothesis, the delay-estimated PLV closely matched the profiles of frequency flexibility in phase-locking measured in Section 2.2.1 (Fig. 6, right).

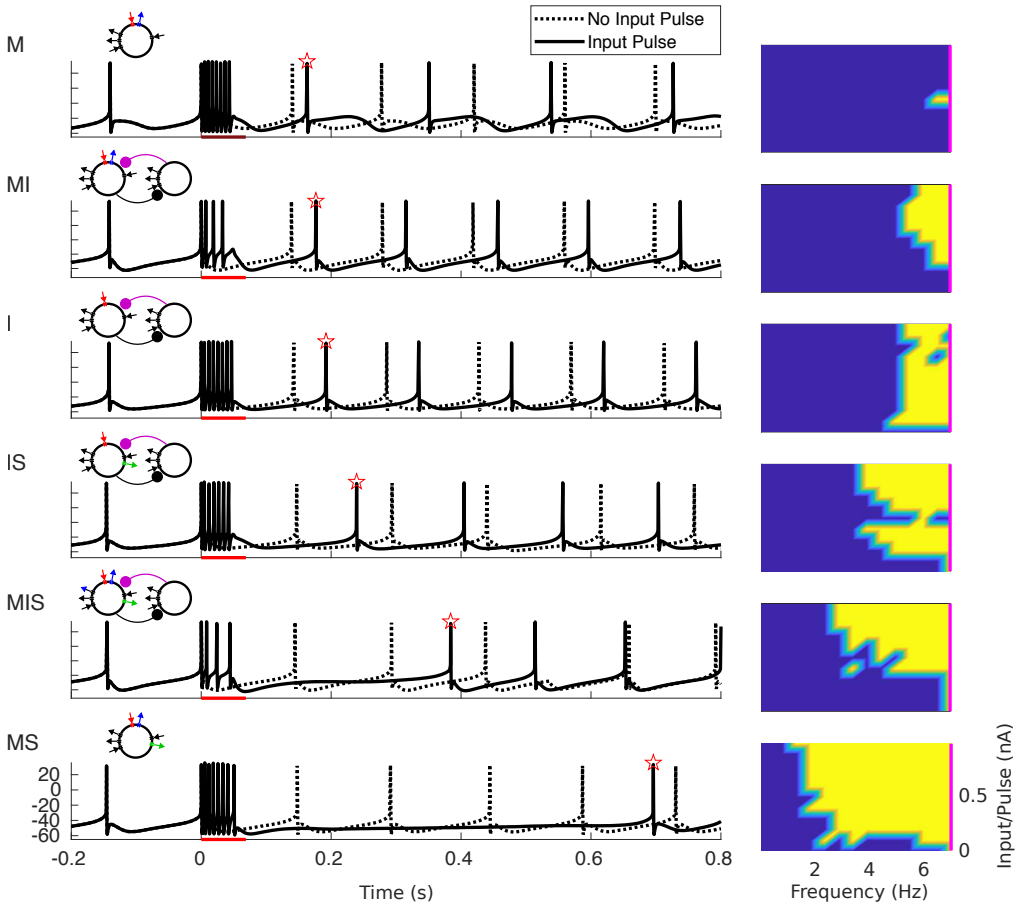

Fig 6. Delay of spiking in response to single pulse determines phase-locking to slow inputs. On the left, voltage traces are plotted for simulations both with (solid lines) and without (dotted lines) an input pulse lasting 50 ms. Red bar indicates the timing of the input pulse; red star indicates the first post-input spike. On the right, the phase-locking value is estimated from the response to a single input pulse using Eqn. 1. Frequency was calculated as 1/(4*(pulse duration)), where pulse duration is in seconds. Input per pulse was calculated by integrating pulse magnitude. The magenta line indicates 7 Hz.

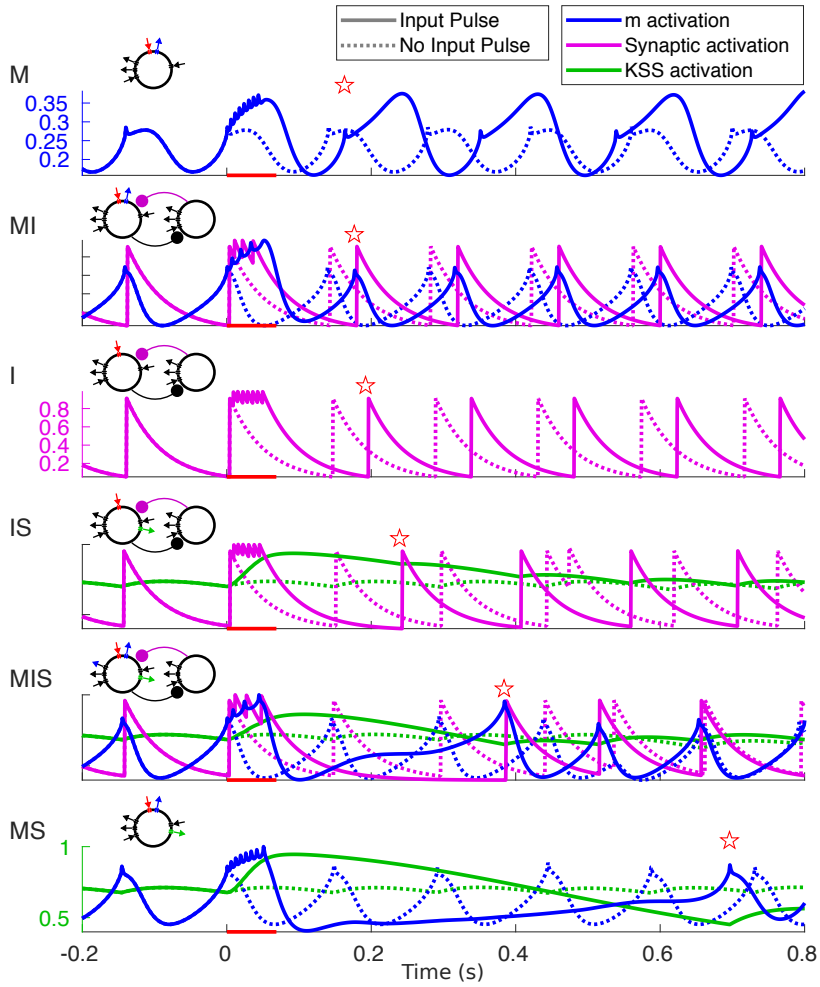

Fig 7. Buildup of outward currents in response to input pulses. Activation variables (color) plotted for simulations both with (dotted lines) and without (solid lines) an input pulse lasting 50 ms. Red bar indicates the timing of the input pulse; red star indicates the time of the first post-input spike.

2.3.2 Dynamics of inhibitory currents

To understand how the dynamics of intrinsic and synaptic currents determined the length of the post-input pause in spiking, we examined the gating variables of the three outward currents simulated in our models during both spontaneous rhythmicity and following forcing with a single input pulse (Fig. 7). Plotting the relationships between these currents during the time step immediately prior to spiking (Fig. 8) offered insights into the observed gradient of phase-locking frequency flexibility. Below, we describe the dynamics of these outward currents, from simple to complex.

Synaptic inhibition Model I spiked whenever the synaptic inhibitory current I_{inh}

(Fig. 7, purple) or, equivalently, its gating variable, was sufficiently low. This gating variable decayed exponentially from the time of the most recent SOM cell spike; it did not depend on the level of excitation of the RS cell, and thus did not build up during the input pulse. However, post-input spiking delays did occur because RS and SOM cells spiked for the duration of the input pulse, repeatedly resetting the synaptic inhibitory "clock" – the time until I_{inh} had decayed enough for a spontaneous spike to occur. As soon as spiking stopped (at the end of the input pulse or shortly afterwards – our model SOM interneurons were highly excitable and often exhibited noise-induced spiking after the input pulse), the level of inhibition began to decay, and the next spike occurred one 7 Hz period after the end of the input pulse. For periodic input pulses 1/4 the period of the input rhythm, this suggested that the lower frequency limit f^* of phase-locking for model I was determined roughly by the equation

$$D = \frac{1}{4}\left(\frac{1}{f^*}\right) + \frac{1}{7} \geq \frac{1}{f^*} \quad \Longrightarrow \quad f^* \geq \frac{21}{4} = 5.25,$$

which corresponded to the limit observed for model I in Fig. 3 and Fig. 2.3.1.

m-Current In contrast, model M did not spike when the m-current gating variable reaches its nadir, but during the rising phase of its rhythm (Fig. 7). Since the m-current activates slowly, at this phase the upward trajectory in the membrane potential – a delayed effect of the m-current trough – is not yet interrupted by the hyperpolarizing influence of m-current activation. When the cell received an input pulse, the m-current (blue) built up over the course of the input pulse, but since it is a hyperpolarizing current activated by depolarization whose time constant is longest at ∼-26 mV and shorter at de- or hyperpolarized membrane potentials, this buildup resulted in the m-current rapidly shutting itself off following the input pulse. This rapid drop resulted in a lower trough, and, subsequently, a higher peak value of the m-current's gating variable (because the persistent sodium current had more time to depolarize the membrane potential before the m-current was activated enough to hyperpolarize it), changing the frequency of subsequent STOs. It didn't, however, affect the model's phase-locking in the strong forcing regime; the fast falling phase of the m-current following the pulse kept the post-input delay small (Fig. 7). This "elastic" dynamics offers an explanation for model M's inflexibility: the buildup of m-current during an

input pulse leads to a fast hyperpolarization of the membrane potential, which, in turn, causes rapid deactivation of the m-current and subsequent rapid "rebound" of the membrane potential to depolarized levels, preserving the time of the next spike.

Super-slow K current In models with a super-slow K current, this current, like synaptic inhibition, decayed to a nadir before each spike of the intrinsic rhythm. Unlike synaptic inhibition, $I_{\mathrm{K_{SS}}}$ activation built up dramatically during an input pulse (Fig. 7, green), and decayed slowly, increasing the latency of the first spike following the input pulse substantially (Fig. 2.3.1). This slow-building outward current interacted differently, however, with synaptic and intrinsic θ-timescale currents. In model IS, both I_{inh} and $I_{\mathrm{K_{SS}}}$ decayed monotonically following an input pulse, until the total level of hyperpolarization was low enough to permit another spike. We hypothesized that $I_{\mathrm{K_{SS}}}$ and I_{inh} interacted additively to produce hyperpolarization and a pause in RS cell spiking. In other words, the delay until the next spike is determined by the time it takes for a sum of the two currents' gating variables (weighted by their conductances and the driving force of potassium) to drop to a particular level. The fact that we expect this weighted sum of the gating variables to be nearly the same (having value, say, a^*) in the time t^* before each spike suggests that the two gating variables are negatively linearly related:

$$\begin{aligned} g_{\mathrm{SOM\to RS}} s(t^*)(V(t^*) - E_{\mathrm{K}}) + g_{\mathrm{K_{SS}}} q(t^*)(V(t^*) - E_{\mathrm{K}}) &\simeq a^* \\ \Longrightarrow q(t^*) \simeq -\frac{g_{\mathrm{SOM\to RS}}}{g_{\mathrm{K_{SS}}}} s(t^*) &+ \frac{a^*}{g_{\mathrm{K_{SS}}}(V(t^*) - E_{\mathrm{K}})}. \end{aligned}$$

Plotting the activation levels of these two currents in the timestep before each spike (excluding forced spikes and a handful of outliers) against each other confirmed this hypothesis (Fig. 8, model IS).

The interaction between I_{m} and $I_{\mathrm{K_{SS}}}$ was more complex, as seen in model MS. The pre-spike activation levels of these two currents were not linearly related (Fig. 8, center). When $I_{\mathrm{K_{SS}}}$ built up, it dramatically suppressed the level of the m-current gating variable, biasing the competition between I_{m} and $I_{\mathrm{Na_P}}$ and reducing STO amplitude, and the $I_{\mathrm{K_{SS}}}$ activation had to decay to levels much lower than "baseline" before the oscillator would spike again. Indeed, spiking appeared to require m-current activation to return *above* "baseline", and also to be in the rising phase of its oscillatory dynamics.

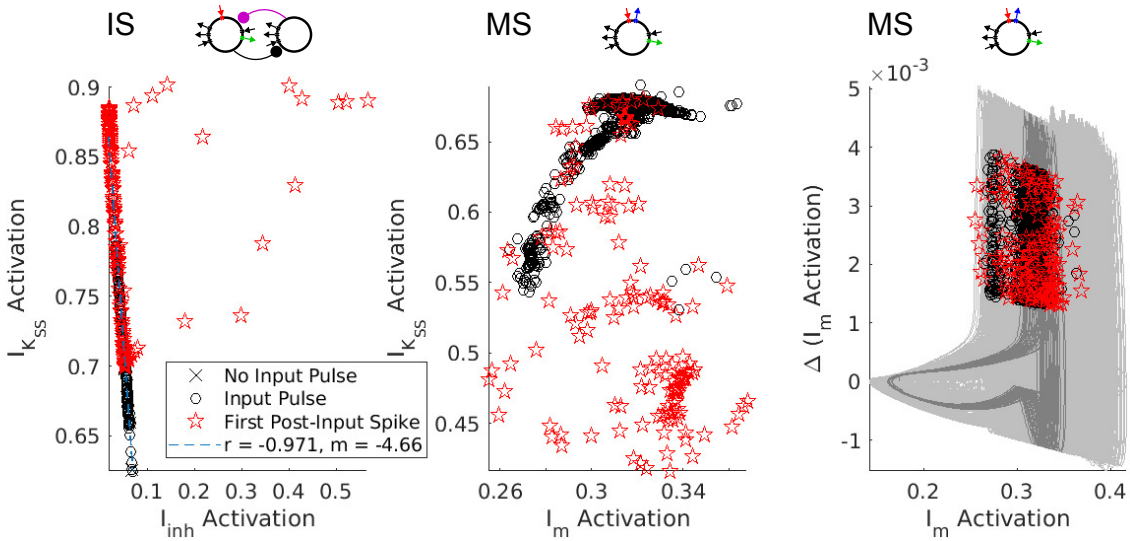

Fig 8. Linear vs. Synergistic Interactions of Inhibitory Currents. Plots of the pre-spike gating variables in models IS and MS. Left, the pre-spike activation levels of I_{inh} and $I_{\mathrm{K_{SS}}}$ in model IS have a negative linear relationship. (Regression line calculated excluding points with I_{inh} activation > 0.1.) Middle, the pre-spike activation levels of I_{m} and $I_{\mathrm{K_{SS}}}$ in model MS do not exhibit a linear relationship. Right, the plotting the activation level of I_{m} against its first difference reveals that pre-spike activation levels are clustered along a single branch of the oscillator's trajectory. (Light gray curves represent trajectories with an input pulse; dark gray curves represent trajectories without an input pulse.

The dependence of spiking on the phase of the m-current activation could be seen by plotting the "phase plane" trajectories of the oscillator – plotting the m activation against its first difference immediately prior to each spike – revealing a branch of the oscillator's periodic trajectory along which pre-spike activation levels were clustered (Fig. 8, right). Plotting the second difference against the first revealed similar periodic dynamics (Fig. S2, top row).

The models containing both synaptic inhibition and m-current exhibited similar dynamics to model MS, with a dependence of spiking on the phase of the rhythm in I_{m} activation being the clearest pattern observable in the pre-spike activation variables (Fig. S2). This suggests that the delay following the input pulse in these models also reflects an influence of θ-timescale STOs, which may exhibit more complex interactions with I_{inh} in model MI, similar qualitatively if not quantitatively to their interactions with $I_{\mathrm{K_{SS}}}$ in models MS and MIS.

3 Discussion

Our results link the biophysics of cortical oscillators to the flexible phase-locking required for auditory and speech segmentation, suggesting that the intrinsic inhibitory currents observed in cortical θ oscillators [47, 48] may enable these oscillators to entrain robustly to θ-timescale fluctuations in the speech amplitude envelope. We trace these oscillators' propensity for flexible phase-locking to synergistic interactions between these currents, and demonstrate that similar oscillators lacking either of these intrinsic currents show markedly less frequency flexibility in phase-locking, regardless of the presence of θ-timescale synaptic inhibition. These findings suggest that synaptic and intrinsic inhibition may tune neural oscillators to exhibit different levels of phase-locking flexibility, allowing them to play diverse roles – from reliable internal clocks to flexible parsers of sensory input – and have consequences for neural dynamics, speech perception, and brain function.

3.1 Mechanisms of phase-locking

For models containing a variety of intrinsic and synaptic currents, spiking delay following a single input pulse was an important determinant of the lower frequency limit of phase-locking in the strong-forcing regime (Fig. 6). A super-slow current, $I_{\mathrm{K_{SS}}}$, aided the ability to phase-lock to slow frequencies in our models, by building up over a slow timescale in response to burst spiking during a long and strong input pulse. The presence of the super-slow K current increased the frequency range of phase-locking, with every model containing $I_{\mathrm{K_{SS}}}$ able to phase-lock to slower periodic inputs than any model without $I_{\mathrm{K_{SS}}}$ (Fig. 3). The fixed delay time of synaptic inhibition seemed to stabilize the frequency range of phase-locking, with the four models containing I_{inh} exhibiting an intermediate frequency range of phase-locking, while the voltage-dependent and "elastic" dynamics of the m-current seemed to do the opposite, with both the narrowest and the broadest frequency ranges of phase-locking occurring in the four model θ oscillators containing I_{m}, and the very narrowest and broadest ranges occurring in the two of these models that lacked I_{inh} (Fig. 3).

Our investigations showed that the flexible phase-locking in models MS and MIS resulted from a synergistic interaction between slow and super-slow K currents,

demonstrated here – to our knowledge – for the first time. We conjecture that this synergy depends on the subthreshold oscillations (STOs) engendered by the slow K current (the m-current) in our models, as was suggested by an analysis of the pre-spike activation levels of the inhibitory currents in models IS and MS. In model IS, there were no STOs, and the interaction between θ-timescale inhibition (which was synaptic) and $I_{\mathrm{K_{SS}}}$ was additive, so that spikes occurred whenever the (weighted) sum of these gating variables dropped low enough (Fig. 8). In models MIS and MS, where STOs resulted from interactions between the m-current and the persistent sodium current, spiking depended not only on the level of activation of the m-current, but also on the phase of the endogenous oscillation in m-current activation (Fig. 8).

For all models, the frequency flexibility of phase-locking to periodic inputs translated to the ability to phase-lock to quasi-rhythmic (Fig. 4) and speech (Fig. 5) inputs. While it is reasonable to hypothesize that this is the result of the mechanism of phase-locking in the regime of strong forcing, it is important to note that imperfect phase-locking in our models resulted not only from "extra" spikes in the absence of input (as predicted by this hypothesis), but also from "missed" spikes in the presence of input (Fig. 4). An understanding of these "missed" spikes may depend on the properties of our oscillators in the weak-forcing regime.

Phase-locking of neural oscillators under weak forcing has been studied extensively [52–56]. In this regime, a neural oscillator stays close to a limit cycle during and after forcing, and as a result the phase of the oscillator is well-defined throughout forcing. Furthermore, the change in phase induced by an input is small (less than a full cycle), can be calculated, and can be plotted as a function of the phase at which the input is applied, resulting in a phase-response curve (PRC). Our results pertain to a dynamical regime in which PRC theory does not apply, since our forcing is strong and long enough that our oscillators complete multiple cycles during the input pulse, and as a result the phase at the end of forcing is not guaranteed to be a function of the phase at which forcing began. Furthermore, in oscillators which contain $I_{\mathrm{K_{SS}}}$, the dynamics of this slow current adds an additional dimension, which makes it impossible to describe the state of these oscillators in terms of a simple phase variable. Not only the phase of the oscillator, but also its amplitude (which is impacted by the activation of $I_{\mathrm{K_{SS}}}$), determine its dynamics.

Previous work has illuminated many of the dynamical properties of the θ-timescale m-current. The addition of an m-current (or any slow resonating current, such as an h-current or other slow non-inactivating K current) changes a neuron from a Type I to a Type II oscillator [64, 65]. The generation of membrane potential resonance (and subthreshold oscillations) by resonating currents is well-studied [47, 66, 67], and recently it has been shown that the θ-timescale properties of the M-current allow an E-I network subject to θ forcing to precisely coordinate with external forcing on a γ timescale [59]. While STOs play an important role in the behaviors of our model oscillators, subthreshold resonance does not automatically imply suprathreshold resonance or precise response spiking [68]. Thus, our results are not predictable (either *a priori* or *a posteriori*) from known effects of the m-current on neuronal dynamics.

Larger (synaptic) inhibition-paced networks have been studied both computationally and experimentally [50, 69–72], and can exhibit properties distinct from our single (RS) cell inhibition-paced models: computational modeling has shown that the addition of E-E and I-I connectivity in E-I networks can yield frequency flexibility through potentiation of these recurrent connections [70, 72]; and experimental results show that amplitude and instantaneous frequency are related in hippocampal networks, since firing by a larger proportion of excitatory pyramidal cells recruits a larger population of inhibitory interneurons [71], a phenomenon which may enable more frequency flexibility in phase-locking. This raises the question of why the brain would select phase-locking flexibility in single cells vs. networks. One possible answer is energetic efficiency. If flexibility in an inhibition-paced oscillatory network depends on recruiting large numbers of inhibitory interneurons, it may be more efficient to utilize a small number of oscillators, each capable (on its own) of entrainment to quasi-rhythmic inputs containing a large range of instantaneous frequencies.

3.2 Functional implications for auditory and speech processing

Our focus on the θ timescale is motivated by results underscoring the prominence of theta rhythms in the spontaneous and stimulus-driven activity of primate auditory cortex [41, 73–75], by evidence for the (causal [37–40]) role of δ/θ frequency speech-brain entrainment in speech perception [30–37, 40], and by theories suggesting a functional

role for cortical θ oscillations in segmenting auditory and speech input at the syllabic timescale [4, 9–11, 14, 37, 40, 75–77]. Our results suggest that the types of inhibitory currents pacing cortical θ oscillators with an intrinsic frequency of 7 Hz determine these oscillators' ability to phase-lock to the (subcortically processed [63]) amplitude envelopes of continuous speech. While an oscillator with an intrinsic frequency of 3 Hz might do an equally good job of phase-locking to strong inputs with frequencies between 3 and 9 Hz, this does not seem to be the strategy employed by the auditory cortex: the frequencies of (low-frequency) oscillations in primate auditory cortex are $\sim$1.5 and $\sim$7 Hz, not 3 Hz [41]; existing experimental [41, 78] and computational [79] evidence suggests that cortical δ oscillators are unlikely to be driven at θ frequencies even by strong inputs; and MEG studies show that across individuals, speech comprehension is high when cortical frequencies are the same as, or higher than, speech envelope frequencies, and becomes poorer as this relationship reverses [80].

How neural phase-locking to the speech envelope translates to the determination of segmental boundaries (if indeed this is a computational objective of speech processing), and to the temporal alignment of activity in downstream speech processing circuits with these boundaries, remains an open question. Out of our models, MS comes closest to spiking selectively at the peaks of the speech amplitude envelope, yet it does not perform perfectly. Its phase-locking to speech inputs is much poorer than its phase-locking to synthetic inputs. This is due in large part to the methodological challenge of accurately determining the phase of a signal as broadband and irregular as the amplitude envelope of speech (see Section 4.3.3), but it is also due to both "missed" and "extra" spikes (Fig. 5). Furthermore, phase-locking in model MS depends on tonic excitation, with lower levels of tonic excitation leading to more precise phase-locking but more missed cycles, and higher levels of tonic excitation leading to less precise phase-locking but a lower probability of any cycle being missed (Fig. S3). Whether the observed level of phase-locking is nonetheless functionally adequate for syllabic segmentation depends on a number of factors: on whether the inputs driving syllable-segmenting θ oscillators are pre-processed by other auditory cortical circuits; on whether syllable-segmenting θ oscillators tracking a given auditory channel or feature interact with other θ oscillators tracking the same or different channels or features; and on how syllable-segmenting θ oscillators drive other speech processing circuits. The

tradeoff between precise and reliable phase-locking in model MS may be ameliorated in a *network* of such oscillators, connected synaptically or electrically, exhibiting heterogeneity in resting membrane potentials and/or input gains. The understanding of the dynamics of single (cell) oscillators presented here provides a necessary foundation for future investigations of network interactions.

Our models exhibit the highest level of phase-locking to the amplitude envelope of the mid-vocalic frequencies in speech, suggesting a pattern of entrainment to vocalic nuclei rather than consonantal clusters. These results provide empirical support for hypotheses suggesting that cortical θ oscillators align with speech segments bracketed by vocalic nuclei – so-called "theta syllables" – as opposed to conventional syllables, which defy attempts at a consistent acoustic characterization, but are (usually) bracketed by consonantal clusters [14]. These hypotheses are tied to theoretical frameworks (e.g. TEMPO [4, 51]) proposing that pre-lexical chunking and sampling are mediated by a stimulus-entrainable cortical rhythmic hierarchy [41, 77, 81–83], consisting of γ and β rhythms whose amplitude is modulated by a concurrent θ rhythm in turn modulated by an ongoing δ rhythm [41, 82]. This oscillatory hierarchy, whose timescales mirror the timescales of segments, syllables, and phrases in speech [17, 81, 82, 84–86], is believed to fit an adaptive (multi-scale) window structure to the acoustic signal, scaffolding multiscale processes of speech segmentation, sampling, and decoding [4, 51]. Findings that auditory cortical θ rhythms effect the continuous and active segmentation and grouping of auditory stimuli [75], and that the phase of endogenous $\sim$6 Hz oscillations at sound onset determines the categorization of ambiguous syllables (between /da/ and /ga/) by altering their perceived onset length [60], among others, provide important empirical support. In this framework, "theta-syllables" have an information-theoretic advantage over conventional linguistic syllables: the vocalic nuclei of speech have relatively large amplitudes and durations, making them prominent in noise and reliably identifiable [17]; and windows whose edges align with vocalic nuclei center the diphones that contain the majority of the information for speech decoding, ensuring this information is sampled with high fidelity. These considerations may explain why brain rhythms aid speech comprehension in noisy or otherwise challenging environments [87–89].

This in turn suggests one answer to an important question raised by our results (and

by one of our reviewers) – namely, if flexible entrainment to a (quasi-)periodic input depends on the lengths of the delays induced by the input, why go to the trouble of using an oscillator at all, rather than a cell responding only to sufficiently strong inputs? The major difference between oscillators and non-oscillatory circuits driven by rhythmic inputs is what happens when the inputs cease (or are masked by noise): while a non-oscillatory circuit lapses into quiescence, an oscillator continues spiking at its endogenous frequency. Thus, oscillatory mechanisms can track the temporal structure of speech through interruptions and omissions in the speech signal [14]. This capability is crucial to the adjustment of speech processing to the speech rate, a phenomenon in which brain oscillations are strongly implicated. While (limited) speeding or slowing of *entire* utterances does not affect their intelligibility, altering context speech rate can change the perception of unaltered target words, even making them disappear [90–95]. In recent MEG experiments, brain oscillations entrained to the rhythm of contextual speech persisted for several cycles after a speech rate change [95], with this sustained rhythmic activity associated with altered perception of vowel duration and word identity following the rate change [95]. Multiple hypothetical mechanisms have been proposed to account for these effects: the syllabic rate (as encoded by the frequency of an entrained θ rhythm) may determine the sampling rate of phonemic fine structure (as effected by γ rhythmic circuits) [4, 51]; predictive processing of speech may use segment duration relative to context speech speed as evidence to evaluate multiple candidate speech interpretations [45]; and oscillatory entrainment to the syllabic rate may time relevant (lexical, syntactic, and semantic) calculations, enabling the optimal balance of speed and accuracy in the passing of linguistic information up the processing hierarchy before the arrival of new input – so-called "chunk-and-pass" processing [96].

Recent experiments shed light on the limits of adaptation to (uniform) speech compression, showing that while cortical speech-brain phase entrainment persisted for syllabic rates as high as 13 Hz (a speed at which speech was not intelligible), β-rhythmic activity was abnormal in response to this unintelligible compressed speech [97]. This work suggests that the upper syllabic rate limit on speech intelligibility arises not from defective phase-locking, but from inadequate time for mnemonic or other downstream processes between syllables [97]. This agrees with our finding that the upper frequency boundary on phase-locking extends well above the

upper syllabic rate boundary on speech intelligibility (∼9 Hz), and is largely determined by input strength. Nonetheless, it is noteworthy that task-related auditory cortical entrainment operates most reliably over the 1-9 Hz (syllabic) ranges [73].

We have assumed for simplicity, and in line with prominent hypotheses about θ-rhythmic syllable segmentation, that the speech amplitude envelope drives θ oscillators directly, and that their phase-locking to it is directly relevant to speech processing. However, the cortical θ oscillator is embedded in an oscillatory hierarchy, receiving inputs from deep IB cells embedded in δ-rhythmic circuits [48, 61], and connected via reciprocal excitation to superficial RS cells embedded in γ-rhythmic circuits [48, 79]. In the framework of TEMPO, the θ oscillator is hypothesized to be driven by δ circuits, and to drive γ circuits, with a linkage between θ and γ frequency adjusting the sampling rate of auditory input to the syllabic rate. The crucial facts that our oscillators exhibit more spiking in response to stronger inputs, and that their phase-locking to speech inputs is characterized by an *absence* of spiking in the *pauses* between acoustic features, suggests that the effective interaction between θ and γ-rhythmic circuits is mediated not by excitation, but by inhibition, perhaps via superficial neurogliaform cells excited by deep RS cells.

More broadly, there is evidence that cortical θ oscillators in multiple brain regions, entrained to distinct features of auditory and speech inputs, may implement a variety of functions in speech processing. Different regions of human superior temporal gyrus (STG) respond differentially to speech acoustics: posterior STG responds to the onset of speech from silence; middle STG responds to acoustic onset edges (peaks in the rate of change of the speech amplitude envelope); and anterior STG responds to ongoing speech [98, 99]. Similarly, bilaterally occuring δ/θ speech-brain entrainment may subserve hemispherically distinct but timescale-specific functions, with right-hemispheric phase entrainment [82] encoding acoustic, phonological, and prosodic information [31, 82, 88, 100, 101], and left-hemispheric amplitude entrainment [82] encoding higher-level speech structure [36, 86, 102, 103] and top-down predictions [104–106]. Frequency flexibility may shed light on how these multiple θ oscillations are distinguished, collated, and combined. One tempting hypothesis is that the gradient from flexible to restricted phase-locking corresponds to a gradient from stimulus-entrained to endogenous brain rhythms, with oscillators closer to the sensory

periphery exhibiting more flexibility and reverting to intrinsic rhythmicity in the absence of sensory input, enabling them to continue to couple with central oscillators that exhibit less phase-locking flexibility. It is suggestive that the conductance of the m-current, which is key to flexible phase-locking in our models, is altered by acetylcholine, a neuromodulator believed to affect, generally speaking, the balance of dominance between modes of internally and externally generated information [61, 107–109].

Even the potential for flexible entrainment, however, does not seem to be ubiquitous in the brain. In the hippocampus, for example, the θ rhythm is robustly periodic, exhibiting relatively small frequency changes with navigation speed [110]. Interestingly, the mechanisms of hippocampal θ and the neocortical θ rhythmicity discussed in this paper are very different: while the former is dominated by synaptic inhibition, resulting from an interaction of synaptic inhibition and the h-current in oriens lacunosum moleculare interneurons [46], the latter is only modified by it [48]. Our results suggest that mechanisms like that of hippocampal θ, far too inflexible to perform the segmentation tasks necessary for speech comprehension, are instead optimized for a different functional role. One possibility is that imposing a more rigid temporal structure on population activity may help to sort "signal" from "noise" - i.e., imposing a strict frequency and phase criterion that inputs must meet to be processed, functioning as a type of internal clock. Another possibility is that more rigidly patterned oscillations result from a tight relationship to motor sampling routines which operate over an inherently more constrained frequency range, as, for example, whisking, sniffing, and running are related to hippocampal θ [111, 112].

Along these lines, it is intriguing that model MIS exhibits both frequency selectivity in phase-locking at low input strengths, and frequency flexibility in phase-locking at high input strengths (Fig. 4). Input gain can depend on a variety of factors, including attention, stimulus novelty and salience, and whether the input is within- or cross-modality. A mechanism that allows input gain to determine the degree of phase-locking frequency flexibility could enable the differential processing of inputs based on these attributes. Although from one perspective model MIS is the most physiologically realistic of our models, as neurons in deep cortical layers are likely to exhibit all three outward currents studied in this paper [48], the minimal impact of

synaptic inhibition on these large pyramidal cells suggests that model MS is a functionally accurate representation of the majority (by number) of RS cells in layer 5 [61]. It thus represents the main source of θ rhythmicity in primary neocortex [61], and a major source of cortico-cortical afferents driving "downstream" processing [113, 114]. Its properties may have strong implications for the biophysical mechanisms used by the brain to adaptively segment and process complex auditory stimuli evolving on multiple timescales, including speech.

4 Methods

All simulations were run on the MATLAB-based programming platform DynaSim [115], a framework specifically designed by our lab for efficiently prototyping, running, and analyzing simulations of large systems of coupled ordinary differential equations, enabling in particular evaluation of their dynamics over large regions of parameter space. DynaSim is open-source and all models will be made publicly available using this platform.

4.1 Model equations

Our models consisted of at most two cells, a regular spiking (RS) pyramidal cell and an inhibitory interneuron with a timescale of inhibition like that observed in somatostatin-positive interneurons (SOM). Each cell was modeled as a single compartment with Hodgkin-Huxley dynamics. In our RS model, the membrane currents consisted of fast sodium (I_{Na}), delayed-rectifier potassium ($I_{\mathrm{K_{DR}}}$), leak (I_{leak}), slow potassium or m- (I_{m}), and persistent sodium ($I_{\mathrm{Na_P}}$) currents taken from a model of a guinea-pig cortical neuron [47], and calcium (I_{Ca}) and super-slow potassium ($I_{\mathrm{K_{SS}}}$, calcium-activated potassium in this case) currents with dynamics from a hippocampal model [116]. The voltage $V(t)$ was given by the equation

$$C\frac{dV}{dt} = I_{\mathrm{app}} - I_{\mathrm{Na}} - I_{\mathrm{K_{DR}}} - I_{\mathrm{leak}} - I_{\mathrm{m}} - I_{\mathrm{Na_P}} - I_{\mathrm{Ca}} - I_{\mathrm{K_{SS}}} - I_{\mathrm{inh}}$$

Table 1. Currents.

I_{Na} & $I_{\mathrm{Na,SOM}}$	$g_{\mathrm{Na}} m_{\mathrm{Na}}^3 h \left(V - E_{\mathrm{Na}}\right)$
$I_{\mathrm{K_{DR}}}$ & $I_{\mathrm{K_{DR},SOM}}$	$g_{\mathrm{K_{DR}}} m_{\mathrm{K_{DR}}}^4 \left(V - E_{\mathrm{K}}\right)$
I_{leak} & $I_{\mathrm{leak,SOM}}$	$g_{\mathrm{leak}} \left(V - E_{\mathrm{leak}}\right)$
I_{m}	$g_{\mathrm{m}} n \left(V - E_{\mathrm{K}}\right)$
$I_{\mathrm{Na_P}}$	$g_{\mathrm{Na_P}} m_{\mathrm{Na_P}} \left(V - E_{\mathrm{Na_P}}\right)$
I_{Ca}	$g_{\mathrm{Ca}} s^2 \left(V - E_{\mathrm{Ca}}\right)$
$I_{\mathrm{K_{SS}}}$	$g_{\mathrm{K_{SS}}} q \left(V - E_{\mathrm{K}}\right)$
I_{inh} & I_{exc}	$g_{\mathrm{pre\to post}} s_{\mathrm{pre\to post}} \left(V_{\mathrm{post}} - E_{\mathrm{pre\to post}}\right)$

Table 2. Equilibrium Voltages.

	RS	FS
E_{Na}	40	50
E_{K}	-80	-95
E_{leak}	-65	-70
$E_{\mathrm{Na_P}}$	50	–
E_{Ca}	120	–
$E_{\mathrm{RS\to SOM}}$		0
$E_{\mathrm{SOM\to RS}}$	-95	

where the capacitance $C = 2.7$ reflected the large size of deep-layer cortical pyramidal cells, and I_{app}, the applied current, was given by

$$I_{\mathrm{app}}(t) = g_{\mathrm{app}} \left[\left(\frac{t}{\tau_{\mathrm{trans}}} \chi_{\{t \le \tau_{\mathrm{trans}}\}}(t) + \chi_{\{t > \tau_{\mathrm{trans}}\}}(t) \right) + p_{\mathrm{noise}} W(t) \right]$$

with the transition time $\tau_{\mathrm{trans}} = 500$ ms, the noise proportion $p_{\mathrm{noise}} = 0.25$, and $W(t)$ a white noise process. For SOM cells, the membrane currents consisted of fast sodium ($I_{\mathrm{Na,SOM}}$), delayed-rectifier potassium ($I_{\mathrm{K_{DR},SOM}}$), and leak ($I_{\mathrm{leak,SOM}}$) currents [117]. The voltage $V(t)$ was given by the equation

$$C_{\mathrm{SOM}} \frac{dV}{dt} = I_{\mathrm{app,SOM}} - I_{\mathrm{Na,SOM}} - I_{\mathrm{K_{DR},SOM}} - I_{\mathrm{leak,SOM}} - I_{\mathrm{exc}}$$

where $C_{\mathrm{SOM}} = 0.9$ and $I_{\mathrm{app,SOM}}$, the applied current, is constant in time. The form of each current is given in Table 1; equilibrium voltages are given in Table 2; and conductance values for all six models that will be introduced in *Results: Modeling cortical θ oscillators* (see Figure 1) are given in Table 3.

The dynamics of activation variable x (ranging over h, $m_{\mathrm{K_{DR}}}$, n, $m_{\mathrm{Na_P}}$, s, and q in Table 1) were given either in terms of its steady-state value x_∞ and time constant τ_x by the equation

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x},$$

Table 3. Maximal Conductances.

Model	M	MI	I	IS	MIS	MS
g_{Na}	125	125	125	125	125	125
$g_{\mathrm{K_{DR}}}$	54	54	54	54	54	54
g_{leak}	0.31	0.27	0.78	0.78	0.27	0.27
g_{m}	1.4472	1.4472	0	0	1.4472	1.4472
$g_{\mathrm{Na_P}}$	0.4307	0.4307	0.4307	0.4307	0.4307	0.4307
g_{Ca}	0.54	0.54	0.54	0.54	0.54	0.54
$g_{\mathrm{K_{SS}}}$	0	0	0	0.1512	0.1512	0.1512
g_{app}	-7.1	-6.5	-7.6	-10.5	-9.8	-9.2
$g_{\mathrm{Na,SOM}}$	0	100	100	100	100	0
$g_{\mathrm{K_{DR},SOM}}$	0	80	80	80	80	0
$g_{\mathrm{leak,SOM}}$	0	0.1	0.1	0.1	0.1	0
$I_{\mathrm{app,SOM}}$	0	0.95	0.95	0.95	0.95	0
$g_{\mathrm{RS\to SOM}}$	0	0.075	0.075	0.075	0.075	0
$g_{\mathrm{SOM\to RS}}$	0	0.15	0.15	0.15	0.15	0

or in terms of its forward and backward rate functions, α_x and β_x, by the equation

$$\frac{dx}{dt} = (1-x)\alpha_x - x\beta_x.$$

Only the expressions for m_{Na} differed slightly:

$$m_{\mathrm{Na}}(V) = \alpha_m / \left(\alpha_m + \beta_m\right), \qquad m_{\mathrm{Na,SOM}}(V) = \left[1 + \exp\left((-V-38)/10\right)\right]^{-1}.$$

Steady-state values, time constants, and forward and backward rate functions are given in Table 4. For numerical stability, the backwards and forwards rate constants for q and s were converted to steady-state values and time constants before integration, using the equations

$$x_\infty = \alpha_x \tau_x, \qquad \tau_x = \left(\alpha_x + \beta_x\right)^{-1}.$$

Table 4. Activation variable dynamics.

h	$\alpha_h(V) = 0.07\exp\left(-(V+30)/20\right)$	$\beta_h(V) = \left(\exp\left(-V/10\right)+1\right)^{-1}$
m_{Na}	$\alpha_m(V) = -\frac{V+16}{10(\exp(-(V+16)/10)-1)}$	$\beta_m(V) = 4\exp\left(-(V+41)/18\right)$
$m_{\mathrm{K_{DR}}}$	$\alpha_m(V) = -0.01\frac{V+20}{\exp(-(V+20)/10)-1}$	$\beta_m(V) = 0.125\exp\left(-(V+30)/80\right)$
n	$n_\infty(V) = \left[1+\exp\left(-(V+35)/10\right)\right]^{-1}$	$\tau_n(V) = \frac{1000/(3.3*3^{(34-22)/10})}{\exp\left(\frac{V+35}{40}\right)+\exp\left(\frac{-(V+35)}{20}\right)}$
$m_{\mathrm{Na_P}}$	$m_\infty(V) = \left[1+\exp\left(-(V+40)/5\right)\right]^{-1}$	$\tau_m = 5$
s	$\alpha_s(V) = 1.6\left(1+\exp\left(-0.072(V+65)\right)\right)$	$\beta_s(V) = 0.02\frac{V+51.1}{\exp\left(\frac{V+51.1}{5}\right)-1}$
q	$\alpha_q(C_{\mathrm{Ca}}) = \min\left(0.1C_{\mathrm{Ca}},\quad 1\right)$	$\beta_q = 0.002$
h_{SOM}	$h_\infty(V) = \left[1+\exp\left((V+58.3)/6.7\right)\right]^{-1}$	$\tau_h(V) = 0.225 + 1.125\left[1+\exp\left((V+37)/15\right)\right]^{-1}$
$m_{\mathrm{K_{DR},SOM}}$	$m_\infty(V) = \left[1+\exp\left((-V-27)/11.5\right)\right]^{-1}$	$\tau_m(V) = 0.25 + 4.35\left[1+\exp\left(-\left\lvert V+10\right\rvert/10\right)\right]^{-1}.$

The dynamics of the synaptic activation variable s were given by the equation

$$\frac{ds}{dt} = -\frac{s}{\tau_{\mathrm{D}}} + \frac{1-s}{\tau_{\mathrm{R}}}\left(1 + \tanh\left(\frac{V_{\mathrm{pre}}}{10}\right)\right),$$

with time constants $\tau_{\mathrm{R}} = 0.25$ ms, $\tau_{\mathrm{D,RS\to SOM}} = 2.5$ ms, and $\tau_{\mathrm{D,SOM\to RS}} = 50$ ms. The conductance $g_{RS\to SOM}$ was selected to preserve a one-to-one spiking ratio between RS and SOM cells.

4.2 F-I curves

For these curves, we varied the level of tonic applied current I_{app} over the range from 0 to 200 Hz, in steps of 1 Hz. We measured the spiking rate for the last 5 seconds of a 6 second simulation, omitting the transient response in the first second.

4.3 Phase-locking to rhythmic, quasi-rhythmic, and speech inputs

In addition to the tonic applied current I_{app}, to measure phase-locking to rhythmic, quasi-rhythmic, and speech inputs, we introduced time-varying applied currents. These consisted of either periodic pulses (I_{PP}), variable-duration pulse trains with varied inter-pulse intervals (I_{VP}), or speech inputs (I_{speech}).

The (spike rate adjusted) phase-locking value (PLV, [118]) of the oscillator to these inputs was calculated with the expressions

$$PLV = \left(n_s|MRV|^2 - 1\right)/\left(n_s - 1\right), \qquad MRV = \frac{1}{n_s}\sum_{i=1}^{n_s}\exp\left(\sqrt{-1}\phi_I\left(t_i^s\right)\right),$$

where MRV stands for mean resultant vector, n_s is the number of spikes, t_i^s is the time of the ith spike, and $\phi_I(t)$ is the instantaneous phase of input I at frequency ω.

4.3.1 Rhythmic inputs

Periodic pulse inputs were given by the expression

$$I_{\mathrm{PP}}(t) = g_{\mathrm{PP}}\Sigma_i\chi_{\left\{|t-t_i^*|<=w(s-1)/2s\right\}}(t) * \exp\left(-(st/w)^2\right), \tag{2}$$

Table 5. Varied pulse input (I_{VP}) parameters (see *Methods: Phase-locking to rhythmic and quasi-rhythmic inputs: Inputs* for details).

Input Bandwidth ($= f_{\mathrm{high}} - f_{\mathrm{low}}$)	f_{low}	f_{high}	d_{low}	d_{high}	s_{low}	s_{high}	o_{low}	o_{high}
1	6.5	7.5	0.25	0.3	10	40	0	0.05
1.65	6.175	7.825	0.2375	0.325	10	41	0	0.1
2.3	5.85	8.15	0.225	0.35	9	41	0	0.15
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
13.35	0.325	13.675	0.0125	0.775	1	50	0	1

where $\chi_{\mathrm{S}}(t)$ is the function that is 1 on set S and 0 otherwise, $t_i^* = 2\pi\omega i$ for $i = 1, 2, ...$ is the set of times at which pulses occur, ω is the frequency, $w = 1000d/\omega$ is the pulse width given the duty cycle $d \in (0, 1)$, $*$ is the convolution operator, and s determines how square the pulse is, with $s = 1$ being roughly normal and higher s being more square. For our simulations, we took $d = 1/4$ and $s = 25$, and ω ranged over the set $\{0.25, 0.5, 1, 1.5, \ldots, 22.5, 23\}$. Input pulses were normalized so that the total (integrated) input was 1 pA/s, and were then multiplied by a conductance varying from 0 to 4 in steps of 0.1.

For I_{PP}, the instantaneous phase $\phi_I(t)$ was obtained as the angle of the complex time series resulting from the convolution of I_{PP} with a complex Morlet wavelet having the same frequency as the input and a length of 7 cycles.

4.3.2 Quasi-rhythmic inputs

Variable-duration pulse trains were given by the expression

$$I_{\mathrm{VP}}(t) = g_{\mathrm{VP}} \Sigma_i \chi_{\left\{|t - t_i^* - o_i| <= w_i \frac{(s_i - 1)}{2 s_i}\right\}}(t) * \exp\left(-\left(\frac{s_i t}{w_i}\right)^2\right), \tag{3}$$

where

$$t_i^* = \Sigma_{j=1}^{i} 1000/\omega_j,$$

the frequencies $\{\omega_i\}_1^n$ are chosen uniformly from $[f_{\mathrm{low}}, f_{\mathrm{high}}]$, the pulse width is given by $w_i = 1000 d_i/\omega_i$, the duty cycles $\{d_i\}_1^n$ are chosen uniformly from $[d_{\mathrm{low}}, d_{\mathrm{high}}]$, the shape parameters $\{s_i\}_1^n$ are chosen uniformly from $[s_{\mathrm{low}}, s_{\mathrm{high}}]$, and the offsets $\{o_i\}_1^n$ are chosen uniformly from $[o_{\mathrm{low}}, o_{\mathrm{high}}]$. For our simulations, these parameters are given in Table 5.

Since I_{VP} was composed of pulses and interpulse periods of varying duration, it was

not "oscillation-like" enough to employ standard wavelet and Hilbert transforms to obtain accurate estimates of its instantaneous phase. Instead, the following procedure was used to obtain the instantaneous phase of I_{VP}. First, the times that χ_{VP} went from zero to greater than zero ($\{a_i\}_{i=1}^n$) and from greater than zero to zero ($\{b_i\}_{i=1}^n$) were obtained. Second, we specified the phase of I_{VP} on these points via the function $\phi_I^0(t)$, a piecewise constant function satisfying

$$\frac{d}{dt}\phi_I^0(t) = \sum_{i=1}^{n}\left(\frac{3\pi}{2}\delta_{a_i}(t) + \frac{\pi}{2}\delta_{b_i}(t)\right),$$

where δ is the Dirac delta function. Finally, we determined $\phi_I(t)$ from $\phi_I^0(t)$ via linear interpolation, i.e. by setting $\phi_I(t)$ to be the piecewise linear (strictly increasing) function satisfying

$$\phi_I(0) = 0, \qquad \phi_I\left(a_i\right) = \phi_I^0\left(a_i\right), \qquad \phi_I\left(b_i\right) = \phi_I^0\left(b_i\right).$$

The resulting function $\phi_I(t)$ advances by $\pi/2$ over the support of each input pulse (the support is the interval of time over which the input pulse is nonzero), and advances by $3\pi/2$ over the time interval between the supports of consecutive pulses.

4.3.3 Speech inputs

Finally, speech inputs were comprised of 20 blindly selected sentences from the TIMIT corpus of read speech [62], which contains broadband recordings of 630 speakers of eight major dialects of American English, each reading ten phonetically rich sentences. The 16 kHz speech waveform file for each sentence was processed through a model of subcortical auditory processing [63], which decomposed the input into 128 channels containing information from distinct frequency bands, reproducing the cochlear filterbank, and applied a series of nonlinear filters reflecting the computations taking place in subcortical nuclei to each channel. We selected 16 of these channels – having center frequencies of 0.1, 0.13, 0.16, 0.2, 0.25, 0.32, 0.51, 0.64, 0.81, 1, 1.3, 1.6, 2, 2.6, and 3.2 kHz – for presentation to our computational models, and varied the multiplicative gain of the resulting waveforms from 0 to 2 in steps of 0.1 to obtain inputs at a variety of strengths.

Like varied pulse inputs, speech inputs were not "oscillation-like" enough to estimate their instantaneous phase using standard wavelet and Hilbert transforms. Thus, we used the following procedure to extract the instantaneous phase of I_{speech}. First, we calculated the power spectrum of the auditory cortical input channel derived from the speech waveform, using the Thompson multitaper method. Second, we identified peaks in the power spectrum that were at least 2 Hz apart, and used the 2nd, 3rd, and 4th largest peaks in the power spectrum to identify the frequencies of the main oscillatory modes in the θ frequency band (the largest peak in the power spectrum was in the δ frequency band for the sentences we used). Then, we bandpassed convolved the auditory input with Morlet wavelets at these three frequencies and summed the resulting complex time series, to obtain a close approximation of the θ-frequency oscillations in the input. Finally, we took the angle of this complex time series at each point in time to be the instantaneous phase of the input at that channel.

4.4 Spike-triggered input pulses

To explore the buildup of outward current and delay of subsequent spiking induced by strong forcing, we probed each model with a single spike-triggered pulse. These pulses were triggered by the first spike after a transient interval of 2000 ms, had a pulse duration of 50 ms, and had a form given by the summand in Equation 2 with $w = 50$ and $s = 25$ (i was 1 and t_i was the time of the triggering spike).

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Supplemental Material

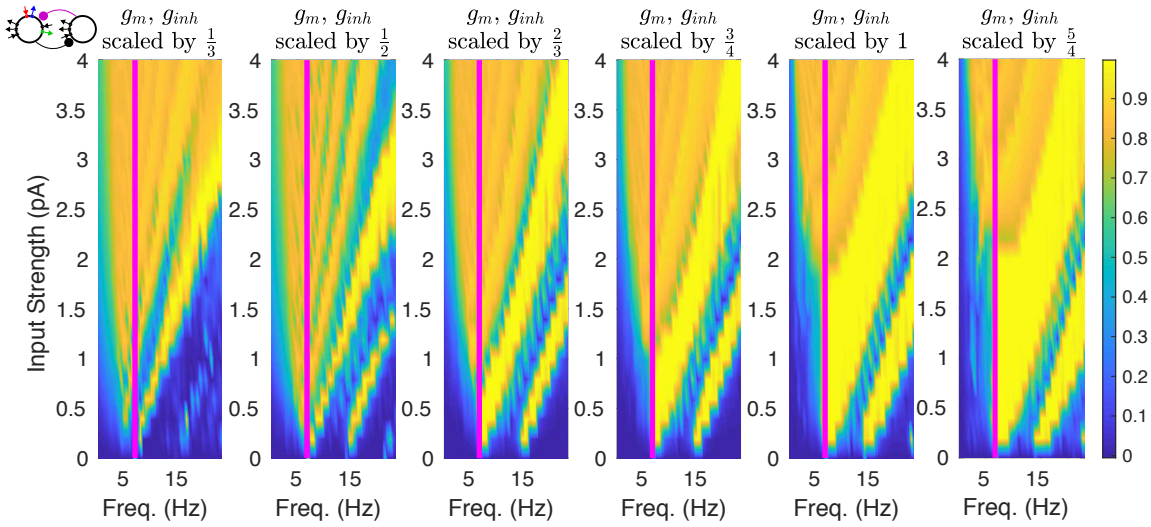

Fig S1. Dependence of One-to-One Phase Locking on Inhibitory Conductance. We multiplied the conductances g_{m} and g_{inh} in model MIS by factors of $\frac{1}{3}$, $\frac{1}{2}$, $\frac{3}{4}$, 1, and $\frac{5}{4}$, and then computed plots of PLV for different input frequencies and strengths, as in Fig. 3. The bright yellow band in each figure, representing the region of one-to-one phase-locking, depends on the size of g_{m} and g_{inh}; both increase from left to right.

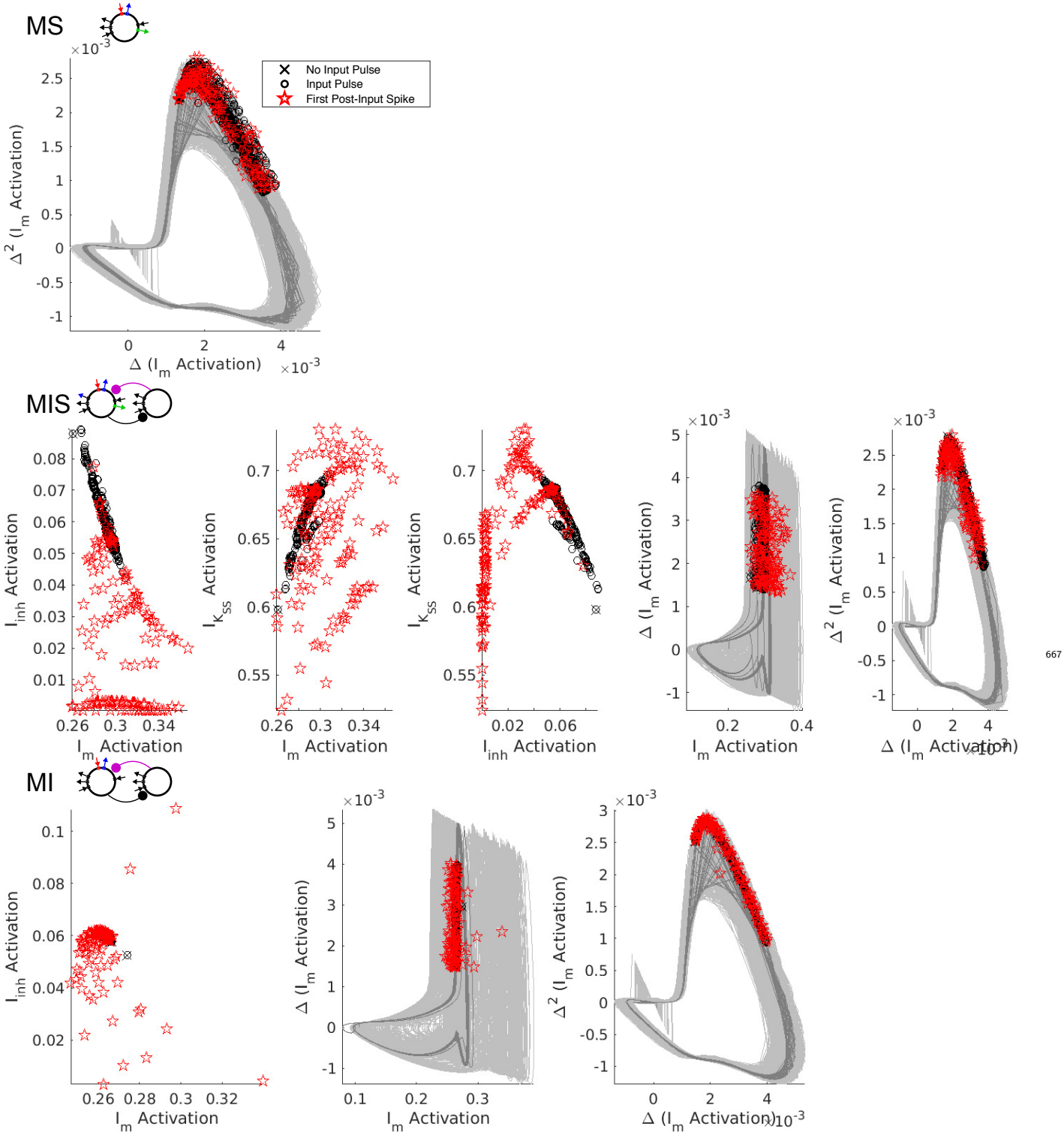

Fig S2. Dynamics of Inhibitory Currents in Models MIS and MI. Plots of the pre-spike gating variables in models MS, MIS, and MI. Top row, plotting the second difference in m-current activation level of against its first difference reveals that pre-spike activation levels are clustered along a single branch of the oscillator's trajectory. Middle row, plots of the relationships between the pre-spike activation levels of I_{inh}, I_{m}, and $I_{\text{K}_{\text{SS}}}$ in model MIS, revealing a dependence on the phase of oscillations in m-current activation. Bottom, plots of the relationships between the pre-spike activation levels of I_{inh} and I_{m} in model MI, again revealing a dependence on the phase of oscillations in m-current activation. (For all plots, light gray curves represent trajectories with an input pulse; dark gray curves represent trajectories without an input pulse.)

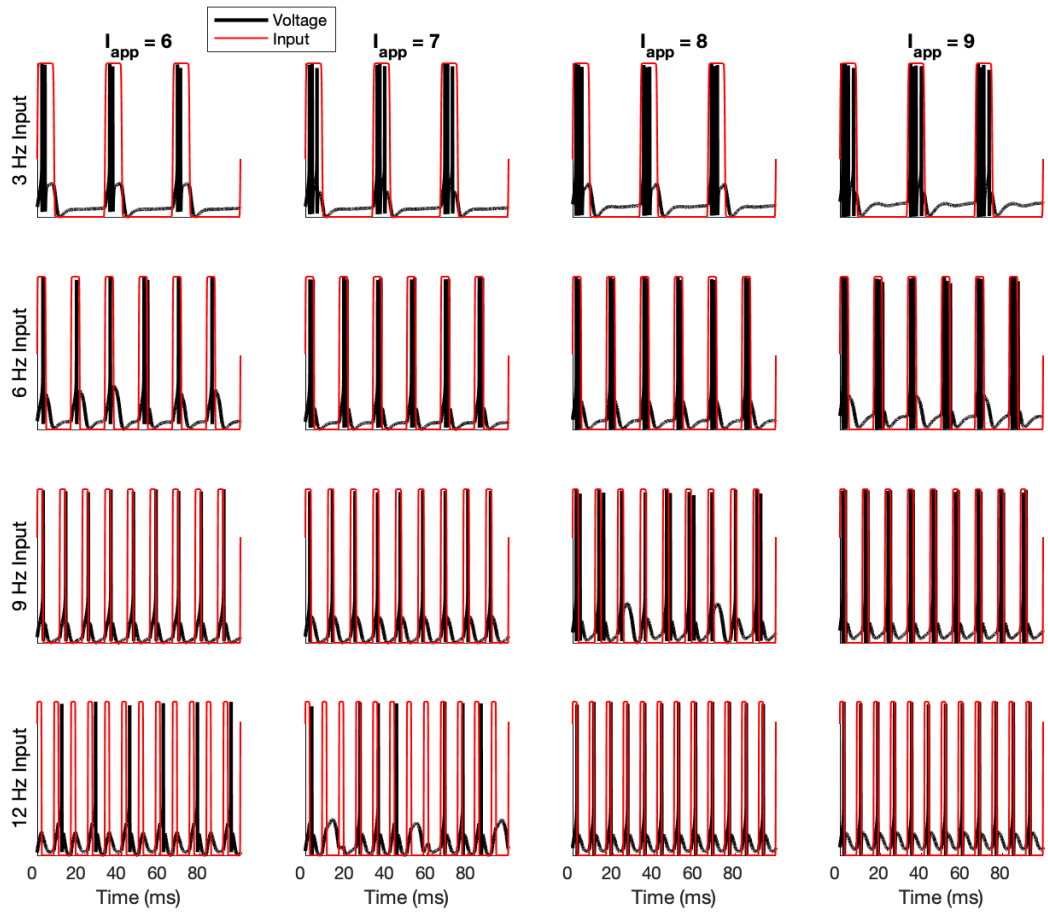

Fig S3. Varying Tonic Input to Model MS. We altered the tonic input strength g_{app} to model MS, and gave periodic pulse inputs of strength $g_{\text{PP}} = 1$ at varying frequencies. For lower levels of tonic input, phase-locking is closer to one-to-one for low frequency inputs, but many high frequency input cycles are "missed"; for higher levels of tonic input, phase-locking is one-to-one for high frequency inputs, but many-to-one for low frequency inputs.

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