Tonically driven and self-sustaining activity in the lamprey hemicord: when can they co-exist?

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Abstract

In lamprey hemisegmental preparations, two types of rhythmic activity are found: slower tonically driven activity which varies according to the external drive, and faster, more stereotypic activity that arises after a transient electrical stimulus. We present a simple conceptual model where a bistable excitable system can exhibit the two states. We then show that a neuronal network model can display the desired characteristics, given that synaptic dynamics - facilitation and saturation - are included. The model behaviour and its dependence on key parameters are illustrated. We discuss the relevance of our model to the lamprey locomotor system.

Keywords: lamprey, dynamical systems, locomotion, recurrent excitation

1 Introduction

Activity in central pattern generators is usually thought to be driven by tonic stimulation. However, activity in motor circuits can in some cases sustain itself by positive feedback in the premotor neural circuitry. Evidence for this comes, for example, from the Xenopus tadpole, where the isolated spinal cord can generate swimming activity both in response to continuous glutamate agonist application and to a transient touch stimulus [8]. In the latter case, a tadpole whose tail is briefly touched initiates a bout of “escape swimming”. In the intact spinal cord of the lamprey, another important vertebrate model system for locomotion, fictive swimming is usually only observed in response to tonic stimulation in the form of bath application of glutamate agonists [2]. However, experiments on preparations which have been transected along the midline, so that only half of the spinal cord (the hemicord) is present, have shown both tonically driven activity and self-sustaining unilateral rhythmic activity in response to a transient stimulus. Specifically, D-glutamate application generates a unilateral rhythm with a frequency of 2-10 Hz, while brief electric stimulation can generate fast rhythmic activity (“locomotor bouts”) which initially has a frequency of up to 20 Hz but progressively slows down. The bouts can outlast the initial stimulus by several minutes [2, 3]. The D-glutamate induced hemisegmental rhythm has been shown to be related to the lamprey’s normal swimming rhythm [2], while the relationship of the locomotor bouts to normal locomotor activity is less clear.

Preparations consisting of just a few hemisegments can display both tonically driven and self-sustaining activity. Since it has been found that blockade of ipsilateral glycinergic inhibition neither abolishes the rhythmic activity in hemisegmental preparations nor changes its frequency
[2], the core of the unilateral burst generator is thought to consist of a population of interconnected excitatory interneurons (EIN).

We examine the necessary conditions for the co-existence of tonically driven rhythmic activity and self-sustaining rhythmic activity in the same network by simulations using a simplified neuronal model. The question we want to address is: If self-sustaining activity is possible at high firing frequencies, tonic excitation acting in concert with recurrent excitation might be expected to lead to even higher activity levels, and possibly loss of rhythmicity. This has not been found to be the case. Rather, tonic activation typically accesses a wide range of activity levels, without triggering stereotypic bouts. How is this possible in a purely excitatory network?

Our approach is based on a conceptual model inspired by dynamical systems theory. We posit that bifurcations occur between cases where the system has either one or three fixpoints, respectively. In the case of one fixpoint, the system will always arrive at a given steady-state frequency regardless of initial conditions. By contrast, in the three-fixpoint case, there will be one stable fixed point corresponding to low spiking activity, one stable fixed point corresponding to a fast-spiking state, and an unstable fixed point in between these. Thus, if the system is started from a frequency below that of the unstable fixpoint, the activity will eventually go to zero or a very low frequency, but if it is started from a higher frequency (for instance, by giving a strong enough transient excitatory stimulus), the system will end up in the fast-spiking steady state. When the initial frequency is below the frequency of the unstable fixed point, the tonic input will determine the steady-state frequency, and this frequency will vary more or less smoothly with the strength of the tonic stimulus. But as soon as the initial frequency is higher than that of the unstable fixed point, the system will go to a high-frequency steady state which is fairly insensitive to the tonic activation. Can this bistability explain the co-existence of low-frequency tonically driven states and self-sustaining locomotor bouts?

In initial simulations using populations of neurons with static synapses, the networks could not exhibit both self-sustaining bout activity and smoothly varying glutamate-driven activity. With the addition of synaptic dynamics, the two types of firing behaviour could be observed in the same network.

2 Methods

We create a simplified model of an EIN using the formalism introduced by Izhikevich [5]. Our chosen parameter values are: \( a = 0.01, b = 0.2, c = -75, d = 9 \); refer to Izhikevich (2003) for explanations of the interpretation of these parameters [5]. The parameter values were chosen to yield cells with realistic current-frequency curves. A more biophysically detailed model, displaying locomotor bouts under various conditions, was presented in a previous paper [4].

The number of EIN cells in a hemisegment is not known. Buchanan et al. (1989) estimated the number to be “at least 20 but possibly much higher”, arguing that at least 20 EIN cells are needed to depolarise a motoneuron to the spiking threshold [1]. We choose to use 50 neurons. Each pair of EINs is connected with a probability of 30%. The cells have AMPA- and NMDA synaptic components. The AMPA synapses, when activated, reach maximum conductance during a single time step (1 ms) with a fast decay, while the conductance of the NMDA synapses reach a maximum after one time step and decay exponentially according to a parameter \( \tau_{NMDA} \), which we vary in the simulations. NMDA synapses are also subject to magnesium block as described in Koch (1999) with a simulated magnesium concentration of 1 mM [6]. As a consequence of the magnesium block, the NMDA channel alone cannot sustain locomotor bouts in the absence of external drive; AMPA transmission is also needed, in our model as well as in experiments [3].

Tonic application of D-glutamate is simulated as a constant baseline activation of AMPA and NMDA synapses in equal proportions. Transient electrical stimulation is simulated by delivering a high-frequency synthetic spike train to each neuron in the network. Cell sizes were randomly chosen between 50% and 200% of a reference size, so that the firing response characteristics were different between neurons. A first round of simulations was run with the model as described so far.
Later, two dynamical aspects were added to the synapse model: facilitation and saturation. Facilitating synapses act as high-pass filters, enhancing the transmission of high-frequency spike trains. In our model, facilitating synapses are implemented with two parameters. The first parameter, the "facilitation time", is the time interval within which two spikes must arrive for the synapse to be facilitated. The second parameter, the "facilitation factor", is the enhancement in synaptic transmission that applies to a spike which arrives within the facilitation time following a previous presynaptic spike. Facilitating synapses have been found in lamprey spinal excitatory interneurons; in one study, the synaptic facilitation was found to be stronger the higher the frequency of a presynaptic spike train [7]. Facilitation was most pronounced at higher stimulation frequencies. At 20 Hz, a facilitation factor of 1.6 was observed. Following this, we choose for our model facilitation times corresponding to 20 Hz or higher frequencies, e.g. a facilitation time of 50 ms. Postulating that synaptic facilitation would be further enhanced for higher frequencies than 20 Hz, we choose to study a higher facilitation factor, namely 3.5. In contrast to synaptic facilitation, synaptic saturation low-pass filters synaptic spike trains. One mechanism of synaptic saturation is competition for neurotransmitter binding sites. Our model of synaptic saturation uses a single parameter: the maximum synaptic activation. The synapse model is linear up to the maximum activation, after which the synaptic conductance cannot increase further. In our model, only the NMDA component of a glutamatergic synapse is saturating. Taking into account the functional role of the NMDA channel as an integrator of presynaptic signals, we choose a saturation level corresponding to 140 single synaptic events.

Sample output from the network is shown in Fig. 1. The left subfigure shows rhythmic activity in the tonic, glutamate-driven mode, while the right subfigure shows activity in the bout mode. As can be observed from the spike rasters, the cells in the network show a clear spread in firing frequency, which is due to variations in cell sizes and to the random connectivity of the network (each neuron receives 16.7±3.2 synapses).
3 Results

Intuitively, it seems unlikely that an excitatory network would display radically different firing modes, like the tonic and bout modes in lamprey hemisegmental preparations. The experimental conditions are precisely the same, except for a glutamate bath chemical stimulation in case of the tonic mode and a transient electrical stimulus in the bout mode. Note that the frequency in the bout mode is much higher, even though the preparation receives no external stimulation after the current stimulus has been removed. Initial simulations using a network model with static synapses did not, for any parameter setting tried, produce a network exhibiting both firing modes. An illustration of a typical result is shown in Fig 3A, where $\tau_{\text{NMDA}}$, a parameter influencing the overall excitability of the network, was varied. To obtain bifurcation plots showing the system fixpoints, we simulated the network for 10 seconds, discarded the first four seconds as a transient and varied the initial activity level, the level of tonic stimulation, and $\tau_{\text{NMDA}}$ between simulations. Fig. 3A shows a family of bifurcation diagrams. Of the 9 plotted diagrams, the four rightmost ones lack unstable points: they have only one steady-state frequency, which varies smoothly with the glutamate level. These correspond to low $\tau_{\text{NMDA}}$ values, ranging from 30 to 120 ms. Here, the decay of the NMDA current is not slow enough to allow for regenerative, self-sustaining activity. At the opposite end of the spectrum, the diagram for $\tau = 270$ ms shows bout activity for all glutamate levels, as long as the initial activity exceeds about 10 Hz. The $\tau = 240$ ms diagram shows a bistable region for glutamate levels between 0.005 and 0.026. In this range, the activity goes to zero or a very low frequency when started at a low frequency, and to a high-frequency state otherwise. For higher glutamate levels, there is a single fixpoint, and the network will always reach a high frequency. The $\tau = 180$ - 210 ms cases are similar. $\tau_{\text{NMDA}} = 150$ ms is a borderline case. Here, no unstable fixpoints exist, but there is a narrow region of glutamate concentrations where the steady-state frequency increases rapidly.

Summarising Fig. 3A, the simulated networks with $\tau < 150$ ms give graded activity in the desired range of 2 to 10 Hz. Bistability is exhibited when $\tau > 150$; when $\tau > 270$ there are persistent bouts in the absence of glutamate. There is no value of $\tau$ where the system exhibits both the desired range of tonic activity and self-sustained bouts.

Next, we introduced synaptic dynamics into the network model. Intuitively, facilitating synapses could be expected to stabilise the self-driven high-frequency bout mode, while leaving a tonic low-frequency mode intact. On the other hand, due to individual variations in the cells’ firing rates, the synaptic facilitation mechanism would not be expected to discriminate cleanly between high and low frequency firing modes. In our simulation experiments, we nevertheless found a range of facilitation parameters where the bout as well as the tonic firing modes were present. However, with facilitation as the only dynamic mechanism of the model synapses, we found the firing frequencies in the bout mode in excess of what has been observed experimentally. Incorporating also synaptic saturation into the model, bout frequencies were found to be reduced, while the tonic firing mode was essentially unaffected. Fig. 2 shows the influence of the synaptic dynamics parameters on both tonic and bout steady-state firing frequencies. The left subfigure shows that for short facilitation times, corresponding to requiring high firing rates for facilitation to occur, the bout firing mode cannot be sustained. For long facilitation times, the low-frequency tonically driven mode disappears in the glutamate-driven case. In between, there is a fairly wide range of facilitation times where both modes are present. This range is indicated by a grey rectangle in the figure. Turning to the effects of synaptic saturation (Fig. 2, right), we note that the tonic mode is largely unaffected by changes in this parameter. The bout mode, in contrast, increases its firing frequency along with the synaptic saturation parameter.

Fig. 3B shows a state diagram of a network where both tonic and bout firing modes exist. This network has $\tau_{\text{NMDA}} = 180$ ms. The firing frequencies of the tonic mode vary smoothly between approximately 0 and 10 Hz, whereas 2-10 Hz was the range observed in an experimental study [2]. For the bout mode, only the zero-glutamate case has been addressed experimentally [3]. In our simulations we get a frequency of around 22 Hz in this case, while frequencies up to approximately 20 Hz were observed in the experimental study.
4 Conclusions

In this study, we have used a minimal numerical model to study an excitatory network in the lamprey hemicord. Our cell model is the two-state Izhikevich model [5], which is parsimonious in that it can describe a wide variety of neuronal firing behaviour using few parameters. Our synaptic model is slightly more detailed, but still implements synaptic dynamics in a simple fashion with few tunable parameters. With this model, we were able to show that two different firing modes - tonic and self-sustained activity - can co-exist in a simulated excitatory network. Crucially, the addition of frequency-dependent dynamics in the form of synaptic facilitation and saturation was found sufficient to replicate the experimental observations we set out to study.

While we have shown that the bout and tonic modes can co-exist in the same network, an additional explanation for the two distinct behaviours, as experimentally observed, may be a type of activity-dependent feedback or fatigue. According to this explanation, high-frequency bout activity would be attributed to current stimulation having a rapid effect, exciting the network before fatigue has developed. Our model does not at present include a fatigue mechanism; adding one would further increase the robustness of separation between bout and tonic modes.

Little in the model presented here is specific to the lamprey system. In fact, it may be taken as a rather generic model of excitable systems exhibiting sharp transitions between high- and low activity states, where the low-activity state exhibits a smooth range, while the high-activity state is more stereotypic. In the case of the lamprey, the evolutionary value of such a graded-or-all system may be to allow an all-out high activity mode, that may be triggered in an escape situation to co-exist with a precisely controllable normal swimming mode.

References


Figure 3: Network activity states. On the x-axes are both glutamate concentrations, on the y-axes firing rates of the network. Left: An early network model exhibiting tonic and burst firing modes for different values of a synaptic parameter; the integration time in the NMDA synaptic components. Squares are stable steady state firing rates, circles are unstable steady state firing rates. Right: Co-existence of burst and tonic activity in a single network model, incorporating synaptic dynamics. Black points are stable steady state firing rates. The grey areas correspond to firing rates where the network has a tendency to decrease its firing, white areas to increasing rates.


Vitae

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Mikael Huss (b. 1974) is a Ph.D. student at the Karolinska Institute and the Royal Institute of Technology in Stockholm, Sweden. His thesis research concerns detailed mathematical modelling of neurons and microcircuits in the lamprey spinal cord. In addition to computational neuroscience, Mikael’s research interests include network-based algorithms for bioinformatics. Mikael Huss has an M.Sc. degree in Biotechnology Engineering, a B.A. degree in Chinese and a licentiate degree in Computer Science.

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