Burst dynamics under mixed NMDA and AMPA drive in the models of the lamprey spinal CPG

Alexander Kozlov [a,1] Anders Lansner [a] Sten Grillner [b]

[a] *Studies of Artificial Neural Systems, Dept. of Numerical Analysis and Computer Science, Royal Institute of Technology, SE–10044 Stockholm, SWEDEN*

[b] *Nobel Institute for Neurophysiology, Dept. of Neuroscience, Karolinska Institute, SE–17177 Stockholm, SWEDEN*

Abstract

The spinal CPG of the lamprey is modeled using a chain of nonlinear oscillators. Each oscillator represents a small neuron population capable of bursting under mixed NMDA and AMPA drive. Parameters of the oscillator are derived from detailed conductance-based neuron models. Analysis and simulations of dynamics of a single oscillator, a chain of locally coupled excitatory oscillators and a chain of two pairs of excitatory and inhibitory oscillators in each segment are done. The roles of asymmetric couplings and additional rostral drive for generation of a traveling wave with one cycle per chain length in a realistic frequency range are studied.

Key words: Locomotion; Spinal cord; Lamprey; Modeling

1 Introduction

The lamprey swims by means of body undulations thus forming a quasisinusoidal wave of a single wavelength that travels along the body from head to tail [3]. This traveling wave is generated by local oscillators in the range of 0.1–10 Hz with intersegmental phase lag that is nearly independent of cycle period. Thus for 100 segments in the lamprey, the intersegmental phase lag is stabilized around 1% of the cycle. In experiments, the brainstem and spinal cord can be maintained *in vitro* while activity in the locomotor CPG is induced by electric or pharmacological stimulation. Patterns emerging during

[1] Corresponding author. Tel.: +46-8-7907784.
E-mail address: akozlov@nada.kth.se (A. Kozlov)

this "fictive swimming" are similar in their characteristics to the ones observed *in vivo*.

Our goal in the current study is to suggest through modeling a plausible implementation of phase and frequency control in the spinal network of lamprey. To this end, we model calcium dynamics in interneurons under mixed NMDA and AMPA drive and explore its consequences for swimming rhythm generation.

2 Description of the cell model

The oscillator equations comprise leakage, NMDA and AMPA inward currents activated synaptically and from the bath, and $\mathrm{K_{Ca}}$ outward current. Calcium enters the unit through NMDA channels. The model is developed by a gradual, step-by-step reduction and simplification of detailed conductance-based models of cells and synapses which have been developed earlier [1,2,4,9]. Thus the oscillator model is sufficiently simple for limited mathematical analysis and fast simulations, and still keeps direct correspondences of its parameters and state variables to characteristics measured experimentally. This makes this model different from previous simplified models [5, 7, 10].

Here, the dynamics of the membrane potential v and the intracellullar calcium concentration u is modeled in dimensionless form as

$$\begin{aligned} dv/dt &= i - v + i_a + i_n + i_k + i_{sa} + i_{sn} + i_{sg}, \quad du/dt = \varepsilon(-u + i_{cn})\,, \\ & i_a = a(e_a - v),\ i_n = np(v)(e_n - v),\ i_k = ku(e_k - v)\,, \\ & i_{cn} = \beta np(v)(e_{cn} - v) + \beta i_{scn},\ p(v) = 1/(1 + 0.014\,\mathrm{e}^{(1-v)/0.12})\,, \end{aligned} \tag{1}$$

where i is the injected current, a and n are the conductances of the bath-activated AMPA and NMDA channels, $k = 4.5$ is the conductance of the calcium-dependent potassium channel, $e_a = 1, e_n = 1, e_k = -0.14, e_{cn} = 1.29$ are the reversal potentials, β is the calcium influx rate, $\varepsilon = 0.016$ is the reciprocal of the calcium time constant, and $p(v)$ is the opening function of the voltage-dependent magnesium block. Synaptic input has two excitatory components, i_{sa} and i_{sn} (AMPA and NMDA, respectively), and one inhibitory component, i_{sg} (glycin),

$$\begin{aligned} i_{sa} &= s_a h(v_{pre})(e_a - v)\,, \\ i_{sn} &= s_n h(w) p(v)(e_n - v), \quad dw/dt = (v_{pre} - w)/\tau_n\,, \\ i_{sg} &= s_g h(v_{pre})(e_g - v), \quad h(v) = 1/(1 + \mathrm{e}^{(0.3-v)/0.1})\,, \end{aligned} \tag{2}$$

where v_{pre} and v are the pre- and postsynaptic membrane potentials, s_a, s_n, s_g are the synaptic conductances, $e_a = 1, e_n = 1, e_g = -0.06$ are the reversal potentials, τ_n is the NMDA receptor activation time constant, and $h(v)$ is the

synaptic transfer function. Synapse contribution to calcium influx is modeled by the current

$$i_{scn} = s_n h(w) p(v)(e_{cn} - v)\,. \tag{3}$$

The cell model (1)–(3) is used for network simulations. All oscillators are identical, only bath drives and synaptic couplings are varied.

3 Results

3.1 Single cell dynamics

The single cell without recurrent excitation is a potential burster under bath NMDA drive. AMPA application controls the frequency of NMDA-induced oscillations so the burst frequency gradually increases with the increase of conductance a or the proportional increase of both n and a. The oscillations occur in a limited range of β, as shown in Fig. 1, so the calcium influx can be neither too high nor too low.

Recurrent excitation increases cell excitability. It shifts the region of oscillations towards smaller values of n so for the strong enough recurrent excitation the oscillations can be observed even without bath NMDA drive (not shown).

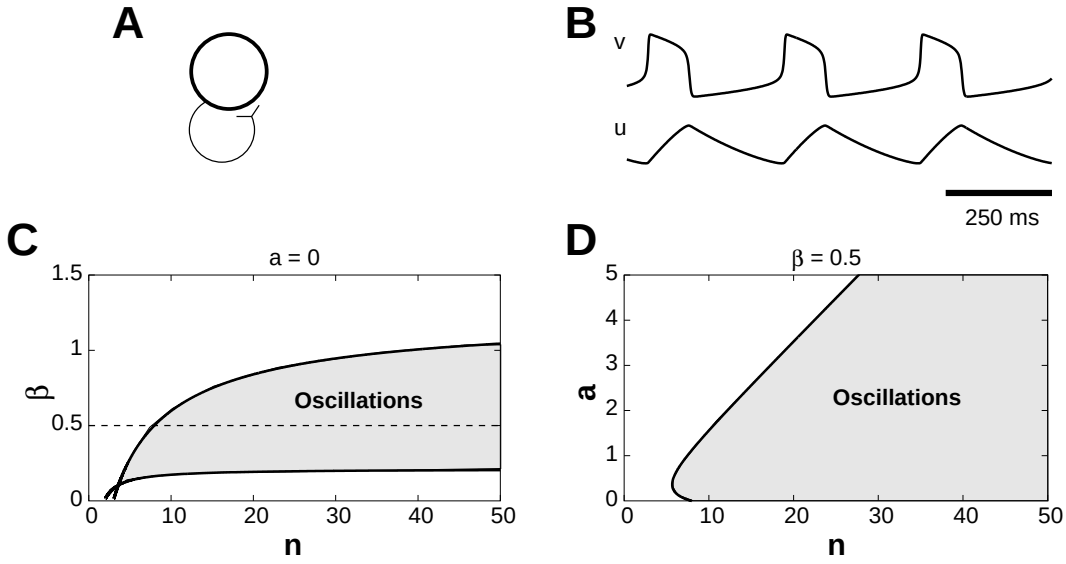

Fig. 1. Single cell dynamics. (A) A cell with recurrent excitation. (B) Typical waveforms of the membrane potential, v, and the intracellular calcium concentration, u. (C, D) Bifurcation diagrams for the model (1) without recurrent excitation. Regions of periodic oscillations are shaded.

3.2 Phase locking

Excitatory synapses are able to synchronize non-identical oscillators for sufficiently strong reciprocal coupling as shown in Fig. 2A. The oscillator with the higher intrinsic frequency due to the extra bath AMPA drive entrains the slower one so their phases get locked with the phase of the former leading. The phase difference is smaller for stronger couplings and it tends to be larger if the NMDA component dominates as shown in Fig. 2B.

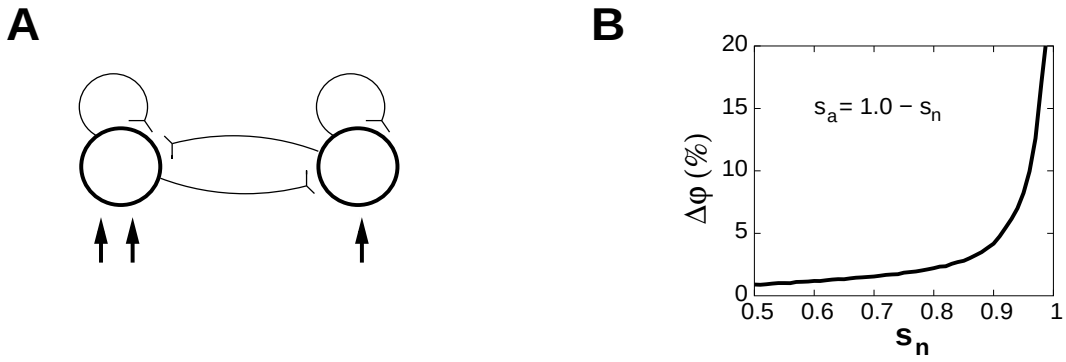

Fig. 2. Synchronization of reciprocally coupled non-identical oscillators. (A) The left oscillator has 10% more bath AMPA drive. (B) Dependence of the phase difference between membrane potentials of the two oscillators, in percents of the cycle duration, on NMDA and AMPA synaptic conductances, s_n and s_a.

3.3 E-network

A linear chain of oscillators with excitatory couplings to nearest neighbours and recurrent excitation, the E-network, models the dynamics of a piece of spinal cord split along the mid-line (L. Cangiano and S. Grillner, personal communication).

As shown in Fig. 3 an E-network with 100 symmetrically coupled oscillators generates forward swimming patterns in the range of 2–6 Hz with intersegmental phase lag between 0.8% and 1.3% if an additional AMPA drive is applied to the most rostral segment of the chain. This implements the 'trailing oscillator' hypothesis suggested earlier [8].

3.4 EI-network

This network consists of two E-networks reciprocally coupled via inhibitory cells as shown in Fig. 4. The EI-network features prominent descending rostrocaudal asymmetry of contralateral inhibitory connections. It is found that this asymmetry is sufficient for generation of traveling waves even without extra rostral drive as shown in Fig. 5A. Results are verified in large-scale simulations [6] as shown in Fig. 5B. This network maintains a one cycle per chain ("body") length phase lag for higher frequencies most efficiently. In the low frequency

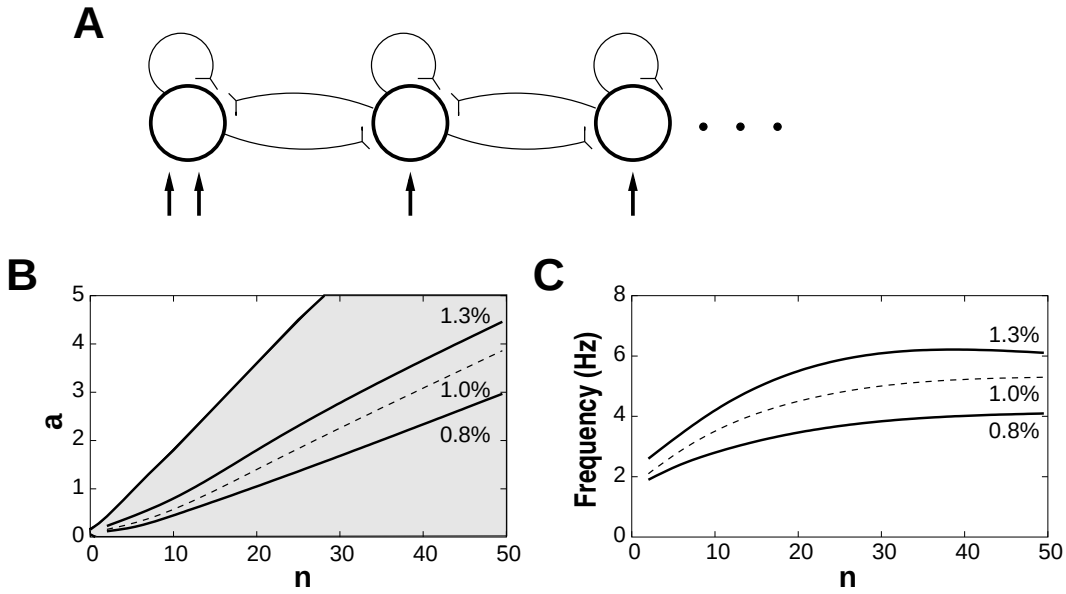

Fig. 3. Coordination of intersegmental phase lag in the chain of excitatory oscillators. (A) The most rostral oscillator has 2% more bath AMPA drive. (B) Oscillations occur within the shaded area. Lines in the region of oscillations show values of n and a corresponding to travelling waves of excitation with intersegmental phase lags of 0.8%, 1.0%, and 1.3%. Frequency of the traveling waves changes along the lines and varies between 2 and 6 Hz (C).

range, additional rostral drive helps to correct the intersegmental phase lag.

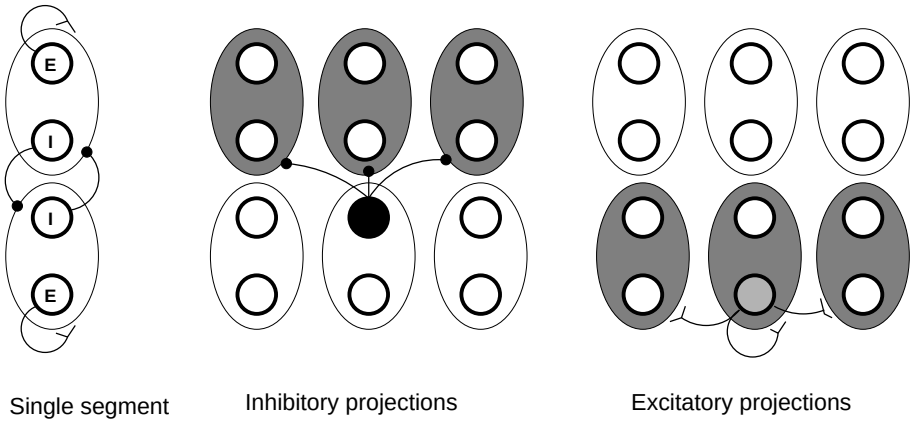

Fig. 4. Configuration of EI-network. One excitatory, E, and one inhibitory, I, oscillators build a hemisegment; two symmetric hemisegments comprise a segment. There are 100 segments in the spinal cord. Excitatory projections are symmetric, inhibitory projections are 50% weaker in the rostral direction.

4 Conclusion

Chains of coupled non-linear network oscillators are shown to reproduce important aspects of the swimming pattern generation in the lamprey spinal

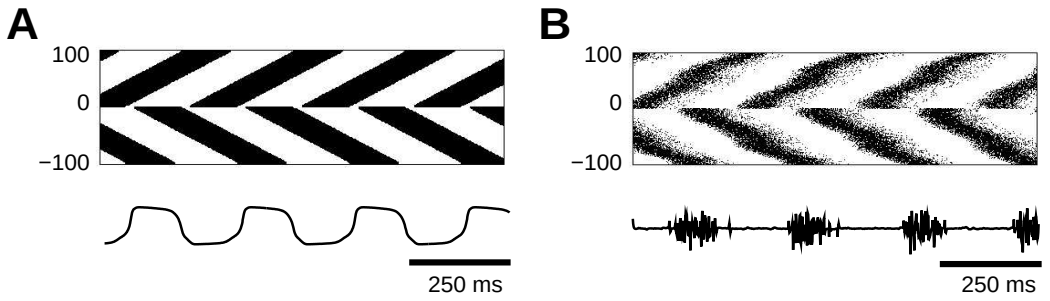

Fig. 5. Comparison of oscillations in simplified (A) and detailed (B) models of the spinal CPG of the lamprey. Time varies along the horizontal line. Excitation propagates from anterior to posterior along the left (from segment 0 to hemisegment -100) and the right (from 0 to +100) sides of the spinal cord in out-of-phase manner. Both models generate one cycle per body length.

CPG. Currents depending on activation of NMDA receptors and the associated calcium dynamics are key determinants of the characteristics of these oscillations. Both E- and EI-networks are capable of producing an adequate swimming coordination, with the EI-configuration being most efficient.

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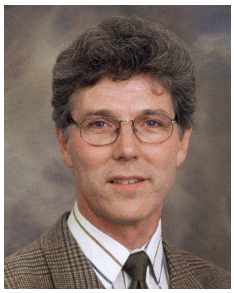
Alexander Kozlov received his Diploma in Radiophysics and Ph.D. in Physics and Mathematics from the University of Nizhny Novgorod, Russia, in 1989 and 1995, respectively. His research in Kungliga Tekniska Högskolan, Stockholm, includes dynamics of control and pattern generating nervous systems, realistic neuron modeling and large-scale simulations.



Anders Lansner received his Ph.D in Computer Science from the Royal Institute of Technology in 1986. He was appointed Professor in Computer Science in 1999 and is manager of the SANS group (Studies of Artificial Neural Systems) founded in 1987. His research interests range from abstract neural network computation to biophysically detailed computational models of specific biological systems and processes.

Sten Grillner is a Professor of the Department of Neuroscience, head of the Division of Neurophysiology and Behavior (The Nobel Institute for Neurophysiology) of Karolinska Institute, Stockholm. His research interest is directed towards an understanding of certain aspects of the cellular and network level and how the different types of neurons combine to form networks which underlie basic modes of coordination such as control of body orientation and locomotion.