Generation of locomotor-like activity in the isolated rat spinal cord by electrical microstimulations driven by an artificial CPG

Sébastien Joucla, Matthieu Ambroise, Timothée Levi, Thierry Lafon, Philippe Chauvet, Lionel Rousseau, Gaëlle Lissorgues, Sylvain Saïghi, Yannick Bornat, Noëlle Lewis, Sylvie Renaud, Blaise Yvert

Abstract— **Neural prostheses may restore functions following lesions of the central nervous system (CNS). Here, we address this challenge in the neonatal rat spinal cord isolated ex vivo. Microelectrode arrays were inserted in the lumbar region to determine optimal stimulation sites to elicit elementary bursting patterns on L2/L5 ventral roots. An artificial CPG implemented on FPGA was built to generate alternating activity and was hybridized to the living spinal cord to drive electrical microstimulation on pre-identified sites. Using this strategy, sustained left-right and flexor-extensor alternating activity on bilateral L2/L5 ventral roots could be generated, comparable to locomotor-like activity elicited by pharmacological application. These results are a first step toward hybrid artificial/biological solutions for the restoration of lost function in the injured CNS.**

I. INTRODUCTION

The isolated lumbar spinal cord houses the circuitry necessary to generate hindlimb locomotor-like activity characterized by left-right and flexor-extensor alternating bursting patterns. Such activity can be elicited by pharmacological application even when only a few segments of the spinal cord are present [1, 2]. Restoration of locomotor activity following a spinal cord lesion can thus be envisioned by artificially activating the spinal circuitry below the lesion. Recent studies have shown that this can indeed be achieved using macroscopic epidural stimulation on the surface of the spinal cord in combination with pharmacological delivery of serotoninergic agonists [3]. Achieving autonomous prostheses not requiring chronic pharmacological agents will require microstimulation at controlled timing delivered to precise intraspinal locations giving rise to well identified activity patterns [4]. Here we address this issue in the rat spinal cord ex vivo.

II. PROCEDURE

A. Spinal cord recording and stimulation

Whole or T7-sectioned spinal cords were isolated from neonatal P1 or P2 Wistar rats. Bilateral L2 and L5 ventral roots were recorded using glass succion electrodes connected to the NeuroPXI system [5]. Neuronexus probes made of 32 microelectrodes distributed over 4 shanks were inserted bilaterally at L1 level. Biphasic current pulses were delivered at each electrode to assess the activity pattern produced on the ventral roots depending on the stimulation location.

B. Hybridization of an artificial CPG to the spinal cord

An artificial CPG inspired from [6] and made of 2 symmetric networks of 4 regular spiking neurons (Izhikevich neuron model [7]) fully interconnected by inhibitory synapses was implemented onto an configurable digital integrated circuit (FPGA). CPG is optimized to cost few digital resources and is computed in real-time (ms resolution). Both sides of this model CPG were interconnected by reciprocal inhibitory synapses and produced alternating rhythmic bursting activity, feeding output spiking neurons each producing only one output spike per burst. This spike triggered a current microstimulation on one site of the probe.

III. RESULTS & CONCLUSION

Two bilaterally located stimulation sites were identified consistently across preparations to specifically elicit synchronous bursting activity on each pair of diagonally opposed L2 and L5 ventral roots (L2l/L5r and L2r/L5l). These sites were hybridized to the output of the artificial CPG, the activity of which drove the four ventral root outputs into full locomotor-like activity. Such activity could be artificially maintained for long periods of time > 10 minutes; CPG period and outputs timing can be controlled by changing the model network parameters. These results indicate that hybrid artificial/biological networks may provide possible solutions for the rehabilitation of lost function of central nervous system.

REFERENCES

[1] J.R. Cazalets, M. Borde, and F. Clarac, "Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat," J Neurosci, vol. 15, (no. 7 Pt 1), pp. 4943-51., 1995.

[2] O. Kjaerulff and O. Kiehn, "Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study," J Neurosci, vol. 16, (no. 18), pp. 5777-94., 1996.

[3] G. Courtine, Y. Gerasimenko, R. van den Brand, A. Yew, P. Musienko, H. Zhong, B. Song, Y. Ao, R.M. Ichiyama, I. Lavrov, R.R. Roy, M.V. Sofroniew, and V.R. Edgerton, "Transformation of nonfunctional spinal circuits into functional states after the loss of brain input," Nat Neurosci, vol. 12, (no. 10), pp. 1333-42, Oct 2009.

[4] J.A. Bamford, C.T. Putman, and V.K. Mushahwar, "Muscle plasticity in rat following spinal transection and chronic intraspinal microstimulation", IEEE Trans Neural Syst Rehabil Eng, vol. 19, (no. 1), pp. 79-83, Feb 2011.

[5] S. Bonnet, J.F. Bêche, S. Gharbi, O. Abdoun, F. Bocquelet, S. Joucla, V. Agache, F. Sauter, P. Pham, F. Dupont, F. Matonti, L. Hoffart, S. Roux, M. Djilas, B. Kolomiets, R. Caplette, F. Chavane, S. Picaud, B. Yvert, R. Guillemaud, "NeuroPXI: A real-time multi-electrode array system for recording, processing and stimulation of neural networks and the control of high-resolution neural implants for rehabilitation", IRBM vol. 33, pp. 55-60, 2012.

[6] A.A. Hill, J. Lu, M.A. Masino, O.H. Olsen, and R.L. Calabrese, "A model of a segmental oscillator in the leech heartbeat neuronal network," J Comput Neurosci, vol. 10, (no. 3), pp. 281-302, May-Jun 2001.

[7] E.M. Izhikevich, "Simple model of spiking neurons", IEEE Transactions on Neural Networks, vol.14, (no.6), pp. 1569- 1572, 2003.

*Resarch supported by ANR Hyrene No ANR-10-BLAN-0316.

S. Joucla, T. Lafon P. Chauvet and B. Yvert are with the Institute for Cognitive and Integrative Neuroscience (INCIA), CNRS and Univ. Bordeaux, UMR5287, Bordeaux, France. (e-mail: sebastien.joucla@u-bordeaux1.fr; thierry.lafon@u-bordeaux1.fr; corresponding author : B. Y., phone: +33 5 40 00 25 73; fax: +33 5 40 00 25 61; e-mail: blaise.yvert@inserm.fr).

L. Rousseau and G. Lissorgues are with ESIEE-Paris Esycom, Noisy-Le-Grand, France (e-mail: l.rousseau@esiee.fr, lissorgg@esiee.fr).

M. Ambroise, T. Levy, N. Lewis, S. Saighi, S. Renaud are with the IMS laboratory, CNRS and Univ. Bordeaux, UMR5218, Talence, France (e-mail: matthieu.ambroise@u-bordeaux1.fr, timothee.levi@ims-bordeaux.fr, sylvain.saighi@ims-bordeaux.fr, yannick.bornat@ims-bordeaux.fr, noelle.lewis@ims-bordeaux.fr, sylvie.renaud@ims-bordeaux.fr).