Introduction to Closed-Loop Neuroscience

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Most neural activity is transient and sequential

- Subcellular biochemical processes.
- Conductance activations and deactivations in membrane ionic currents.
- Switching dynamics among neurons in small circuits.
- Iterations in inhibitory and excitatory closed-loops.
- Activations of voxels as recorded in fMRI setups

Most information processing in the brain is closed-loop

- Voltage interdependence on the active membrane conductances
- Calcium-voltage dependence
- Closed-loop circuitry among single neurons
- Closed-loop circuitry among systems
- Closed-loops between neural activity and behavior
- Subject to subject closed-loop interaction

The nervous system is only partially observable

- We can only record a few variables involved in the overall information processing: V, [Ca^{2+}], bold signal.

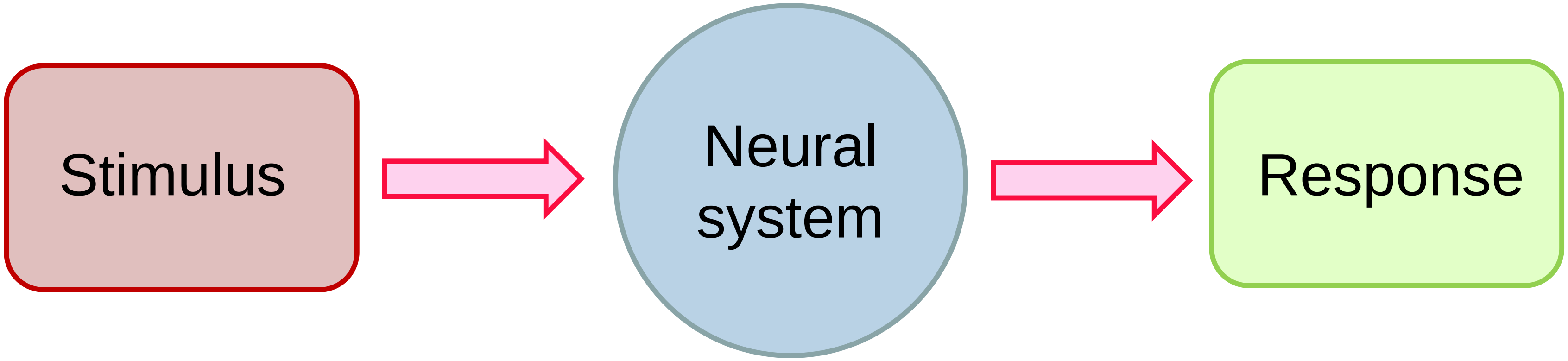
- Neural dynamics is highly nonstationary and adaptive, often working in transient regime.

- Neural systems work with multiple spatial and time scales.

- History-dependent processing, closed-loop processing.

The most prominent experimental approach in Neuroscience

The stimulus-response paradigm



analysis is typically done offline

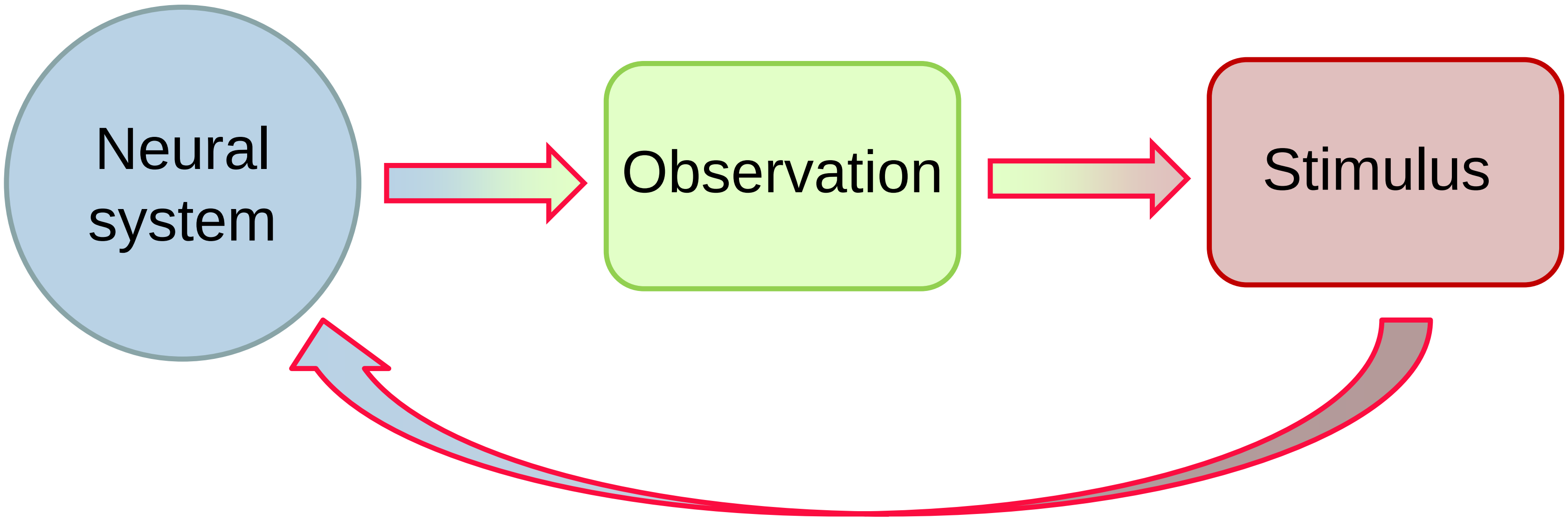
An important need in modern neuroscience research:

Novel experimental protocols that can deal with:

- partial observation
- sequential dynamics
- multiple interacting spatial and temporal scales
- the closed-loop nature of neural information processing

Alternative experimental paradigm:

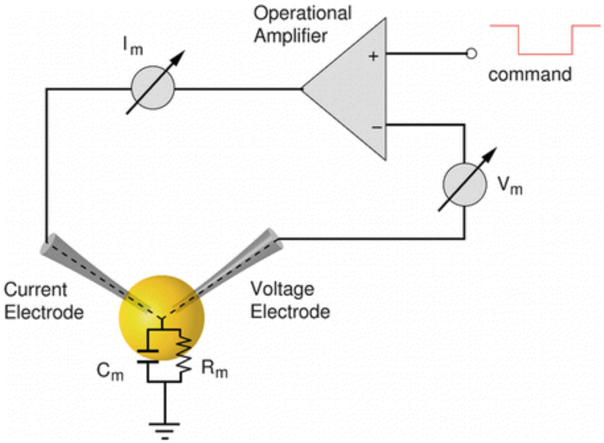
Closed-loop activity-dependent stimulation

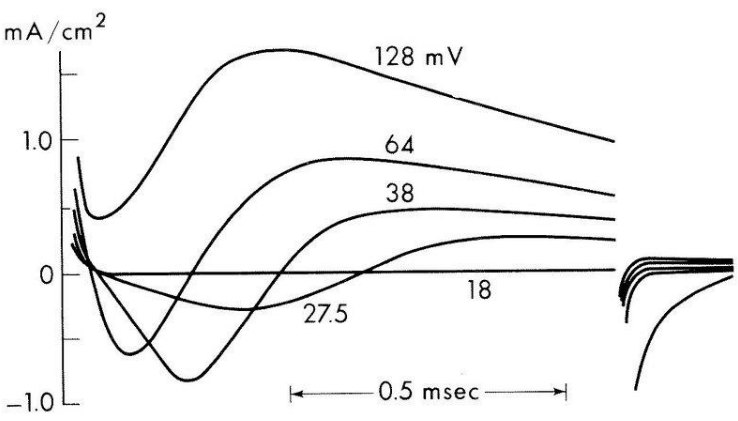


analysis is typically done online

Closed-loop approaches are not that new

- The concept of the **voltage clamp** is attributed to Kenneth Cole and George Marmont in the 1940s.
- Cole discovered that it was possible to use two electrodes and a feedback circuit to keep the cell's membrane potential at a level set by the experimenter.

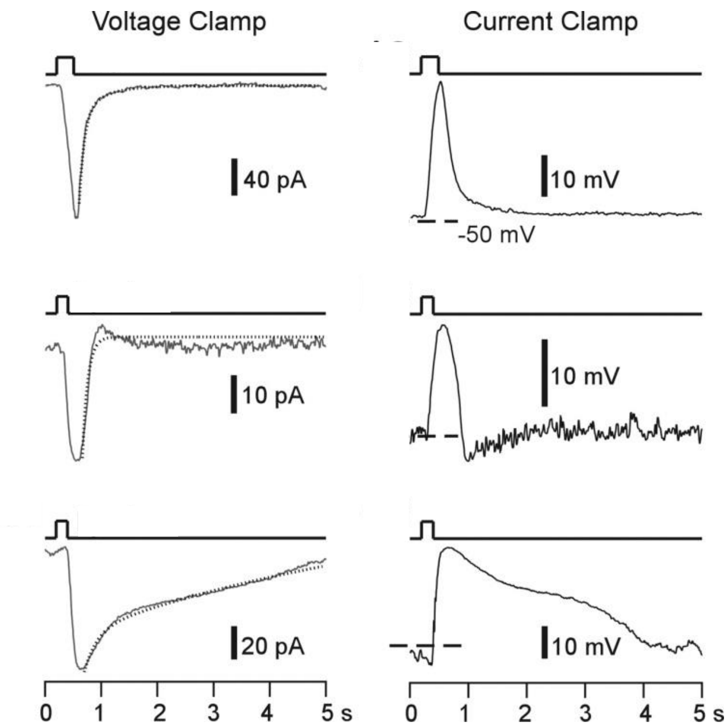




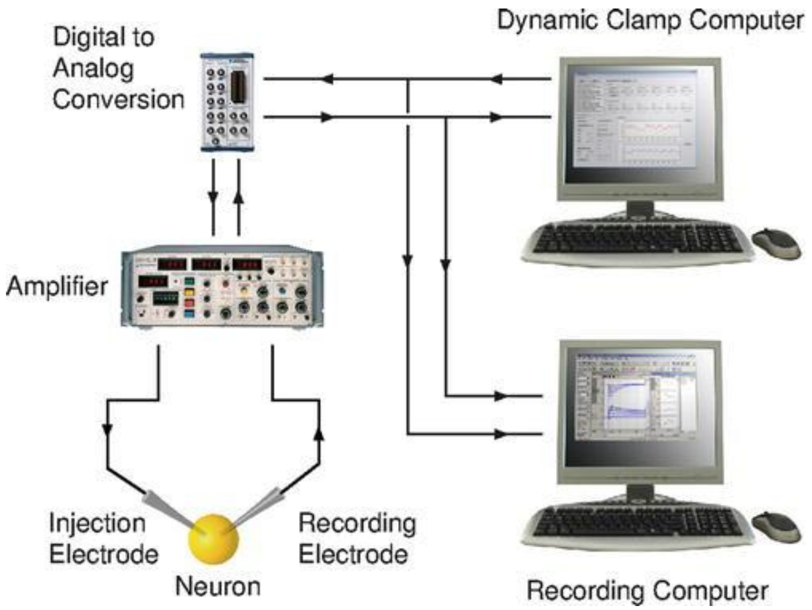
Nowotny T., Levi R. (2014) Voltage-Clamp Technique. In *Encyclopedia of Computational Neuroscience*

Voltage and current clamp

- A current clamp circuit controls the amplitude of the injected current (e.g. via a microelectrode) and allows the voltage to vary.
- Both current clamp and voltage clamp are used to characterize the electrical properties of membranes and ionic channels.



Dynamic clamp



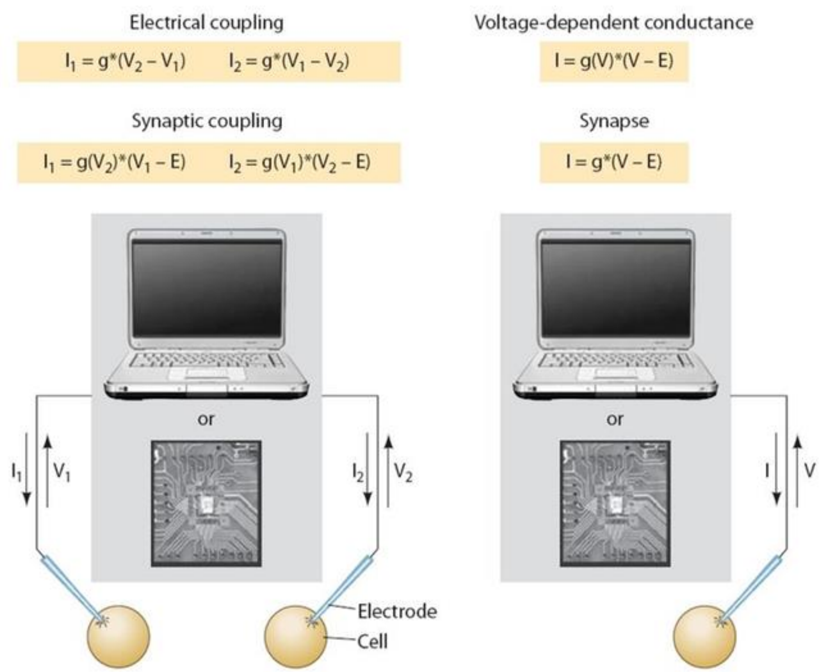
Nowotny T., Varona P. (2014) Dynamic Clamp Technique. In *Encyclopedia of Computational Neuroscience*.

- Dynamic clamp protocols build a voltage-dependent current-injection cycle to introduce artificial membrane or synaptic conductances into living neurons.
- Since 1992, it has been used to investigate a large variety of membrane properties and to create hybrid circuits of living and artificial neurons and synapses.

(Robinson 1991; Robinson and Kawai 1993) called it “Conductance Injection,” (Sharp et al. 1993) named it “Dynamic-Clamp”.

The dynamic clamp closed-loop

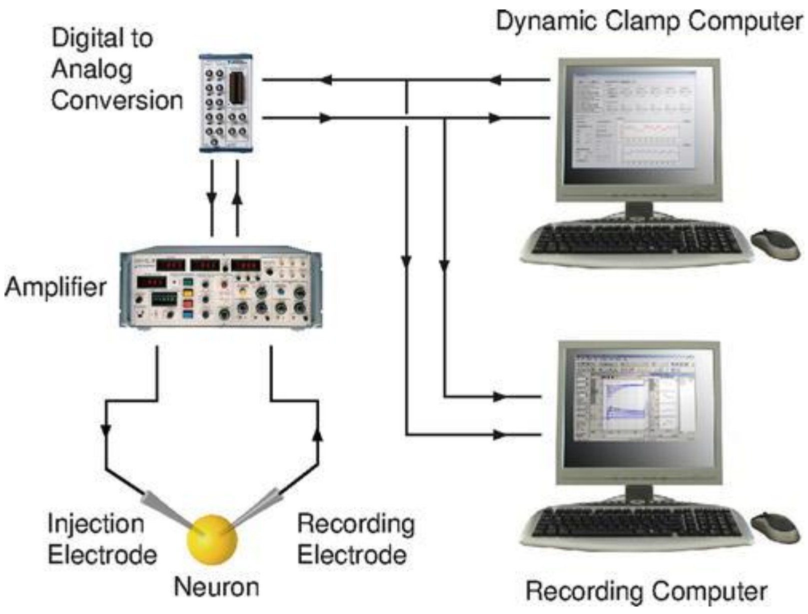
- The membrane potential of one or several neurons is recorded with an electrode and its membrane potential V (or V_1 and V_2) is amplified and sent to a computer.
- The computer runs a model of the membrane or synaptic conductance(s) to be inserted in the living neuron(s), typically in the form of a set of equations and finally delivered as a current I (or I_1 and I_2).



From Goaillard, Marder (2006)

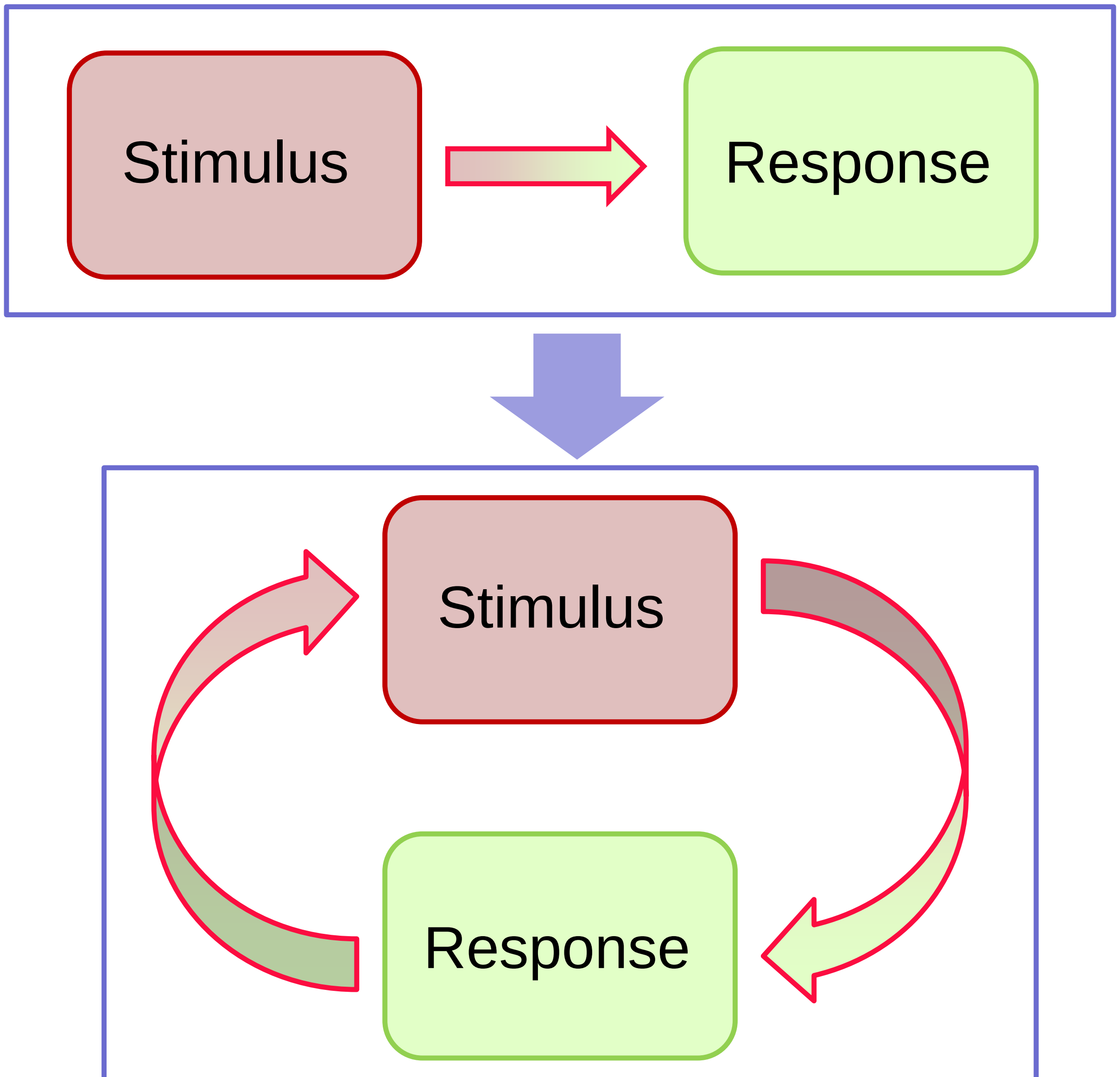
The dynamic clamp closed-loop

- To create a realistic effect, the cycle of reading the membrane potential, the computation of the conductance model and the injection of the dynamic clamp current needs to be completed with an update rate faster than the fastest neural dynamics.
- This often requires real-time software technology.

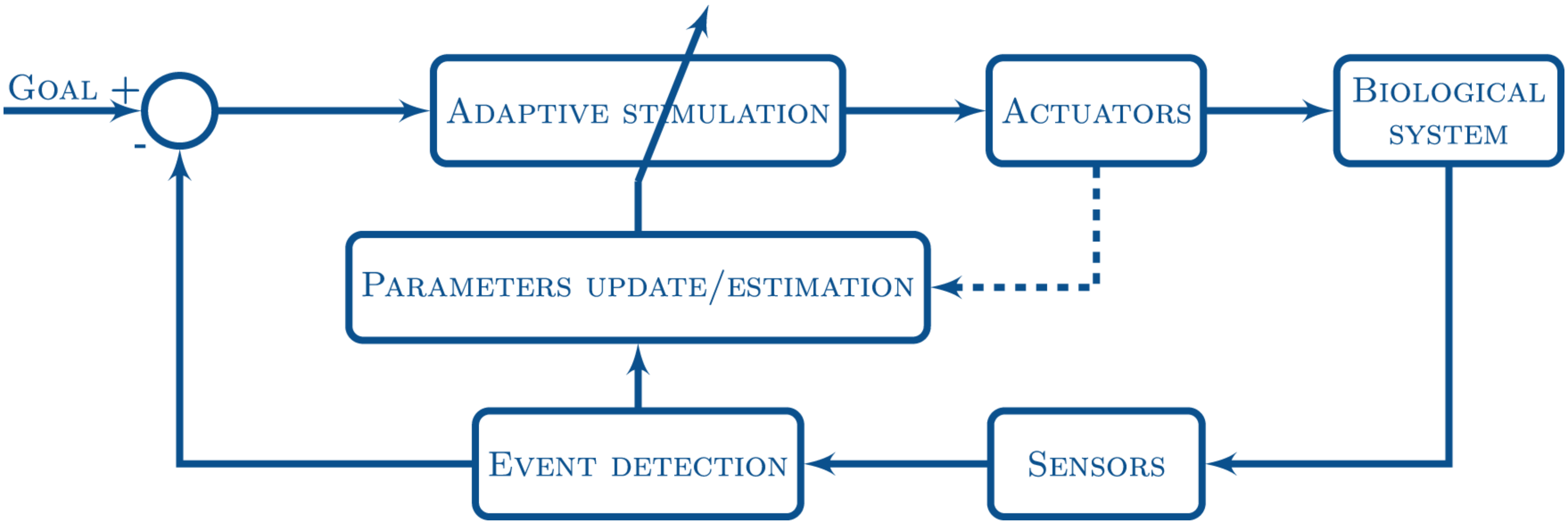


Nowotny T., Varona P. (2014) [Dynamic Clamp Technique. In *Encyclopedia of Computational Neuroscience*.]()

Challenges from the paradigm shift



Closed-loop experiments require a specific design

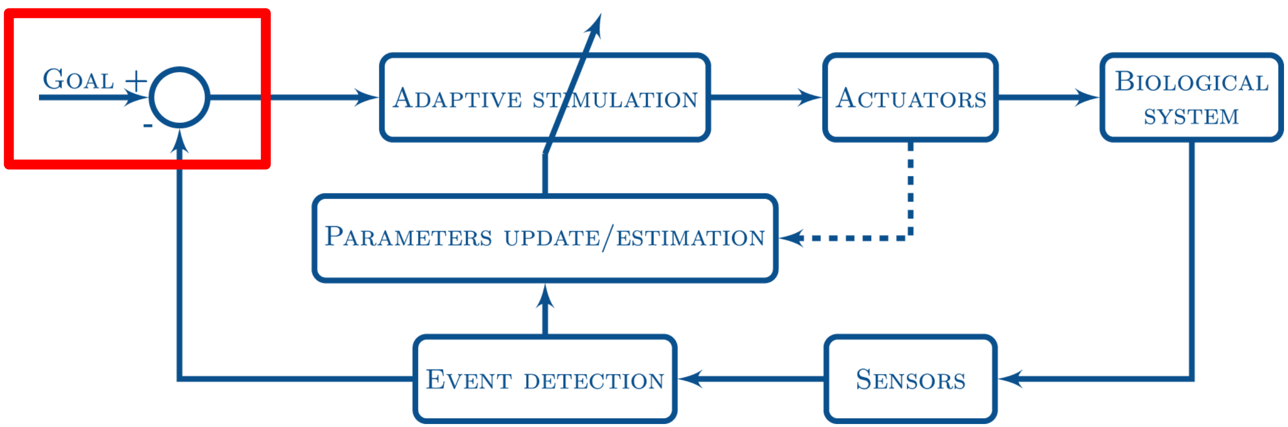


P. Chamorro, C. Muñiz, R. Levi, D. Arroyo. F.B. Rodriguez, P. Varona. 2012. Generalization of the dynamic clamp concept in neurophysiology and behavior. *PLoS ONE* 7(7): e40887.

Closed-loops must be goal-driven

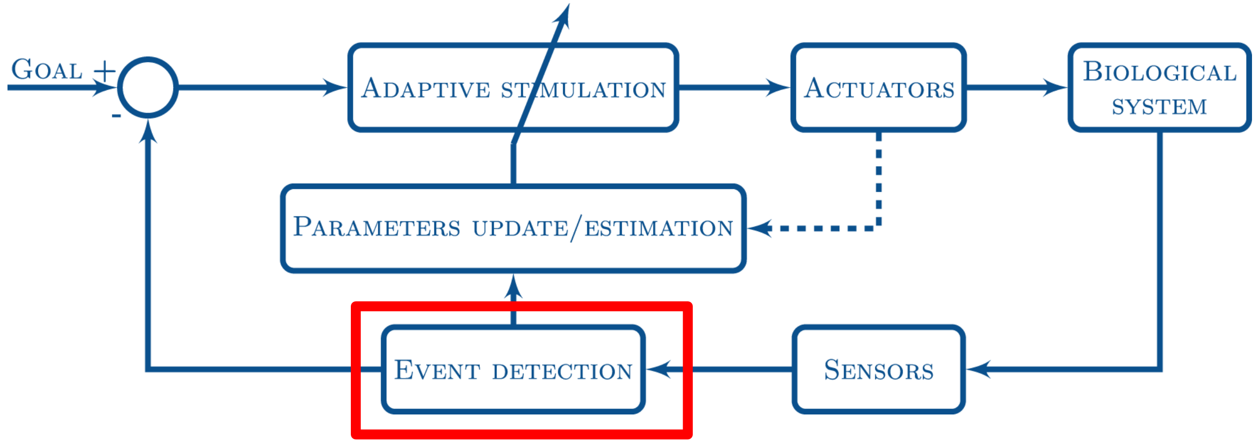
- The closed-loop must be ***goal-driven*** to define a task/goal performance measurement that can be used to drive and evaluate the stimulus exploration.

- Information extracted from the closed-loop can then be used to adapt the stimulation in relation to the goal.



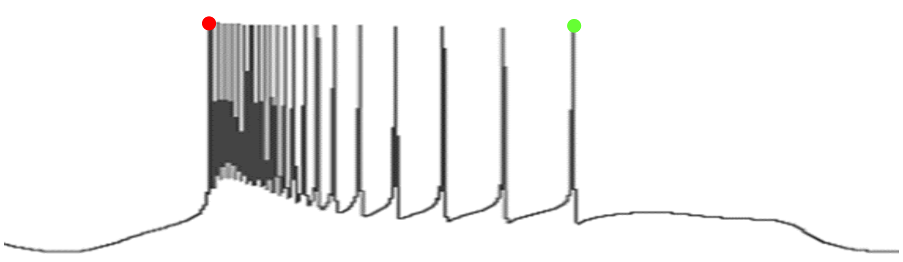
How to design an effective closed-loop

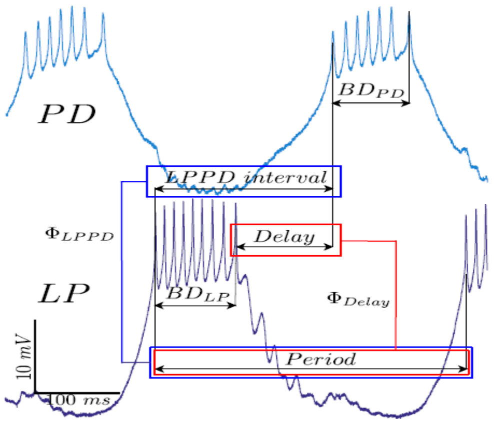
- Closed-loops require real-time **event detection** algorithms:
  - automatic detection of **relevant events for characterizing the neural state**, in relation to the task/goal, and to identify effective stimuli, i.e., feeding into the stimulus exploration strategy.



Event detection may imply processing online and integrating online

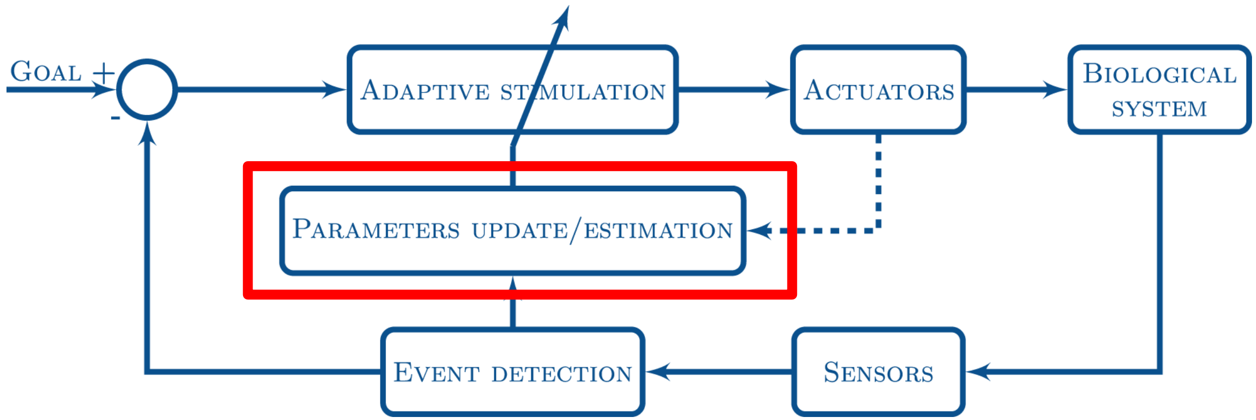
- Real-time **event detection** algorithms:
  - Automatic identification for closed-loop interaction entails online **filtering**, **subevent detection** and the actual **event detection**.
  - For data from **electrical recordings** (intra or extra-cellular electrophysiology and EEG) the primary features are fast voltage transients that give rise to more complex, higher order events: **action potentials**, **post-synaptic potentials**, **bursts** and their features (duration, waveform, count, etc.), **activation levels or sequential features.**





How to design an effective closed-loop

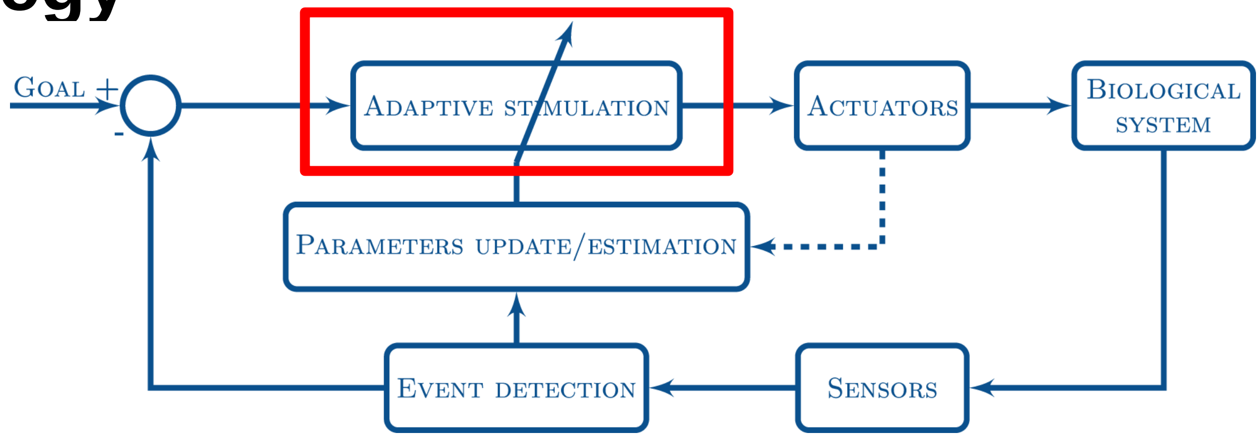
- Closed-loops require **parameters update /estimation** in relation to the goal



  – It can be model driven by a representation that provides **a description of the goal and the system's input/output characteristics** continuously updated through the error between its prediction and the observed activity of the neural system.
  – It can be a **neuron or network model or more abstract, symbolic rule sets** or representations.

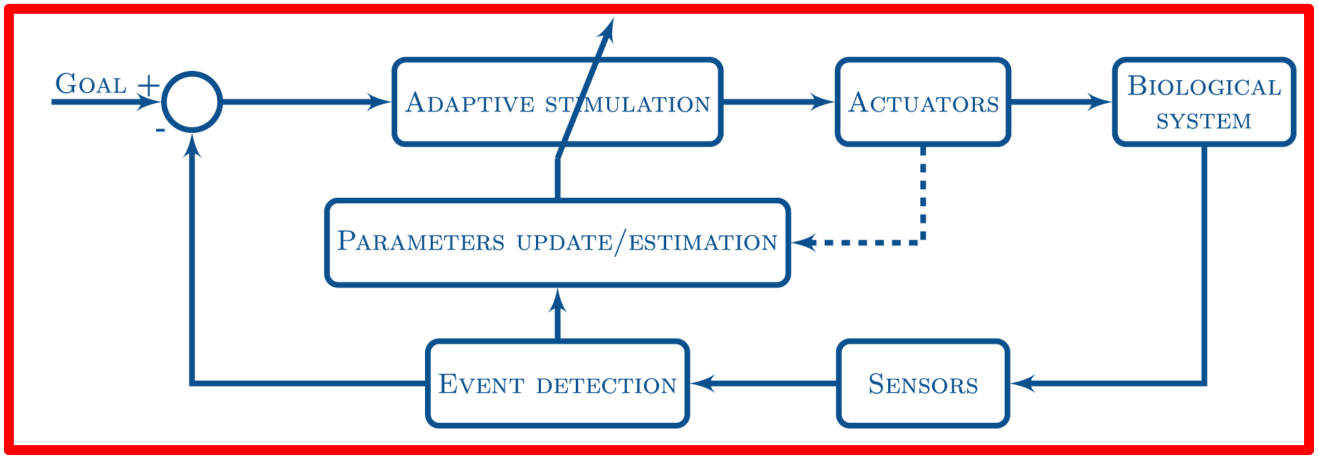
How to design an effective closed-loop

- Closed-loops require **a stimulus exploration strategy**

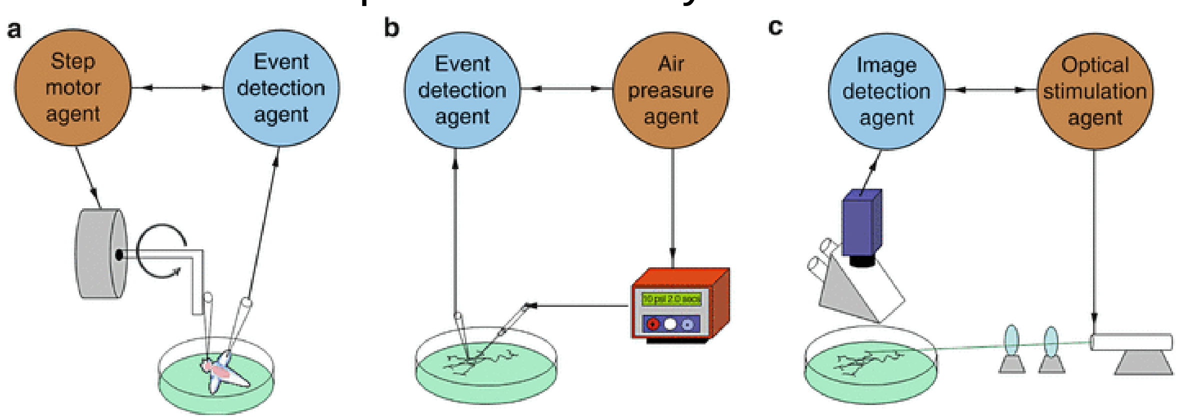


  - The strategy must select appropriate inputs in order to set the operating regime to achieve an active search of the dynamics.
  - This choice of stimuli is essential to deal with the inherent partial observation and take into account the nonstationary and nonlinear aspects of the problem.

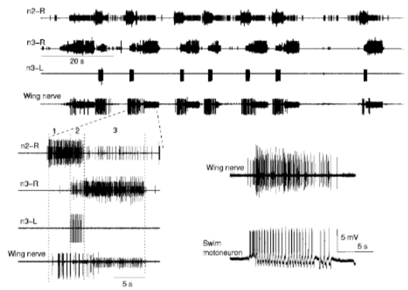
Closed-loop design strategy



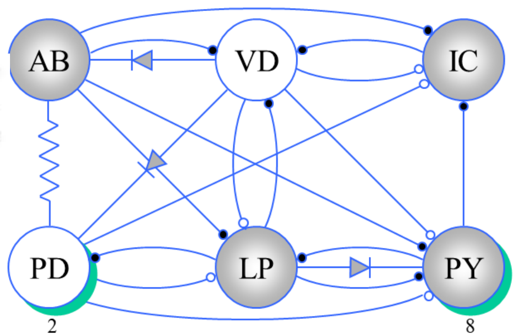
- Signals acquired from a biological system are processed online (data pre-processing and **automatic event detection**). The observed events are compared with the representation of the goal and the parameter estimation in real-time.
- The comparison outcome is used to **adjust the adaptive stimulation** that controls the input to the biological system. A copy of the stimulation commands can be send back to the model to enable predictions of system behaviour for the next cycle.



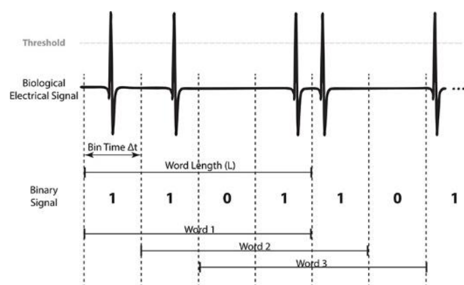
Closed-loops can be applied in multiple scales



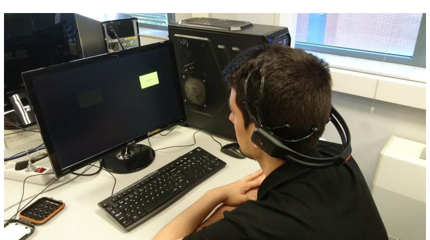
Clione limacina:
Sequential dynamics in the sensory-motor transformation

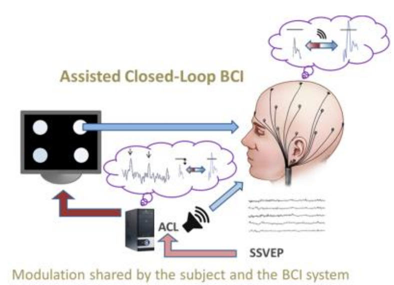


Carcinus maenas, Lymnaea stagnalis:
Dynamical invariants in central pattern generator rhythms



Gnathonemus petersii
Sequential coding in electrolocation and electrocommunication





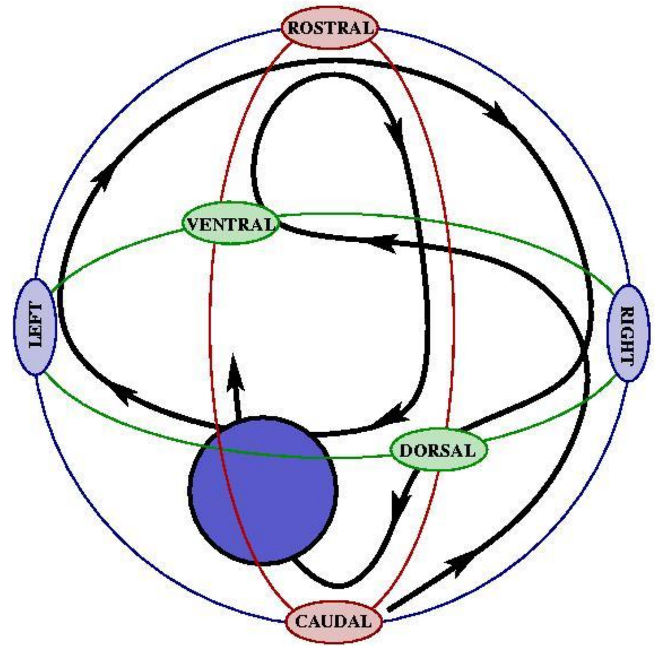
Humans
Visually evoked potentials in brain-computer interfaces

Clione limacina sensorimotor transformation

Routine Swimming

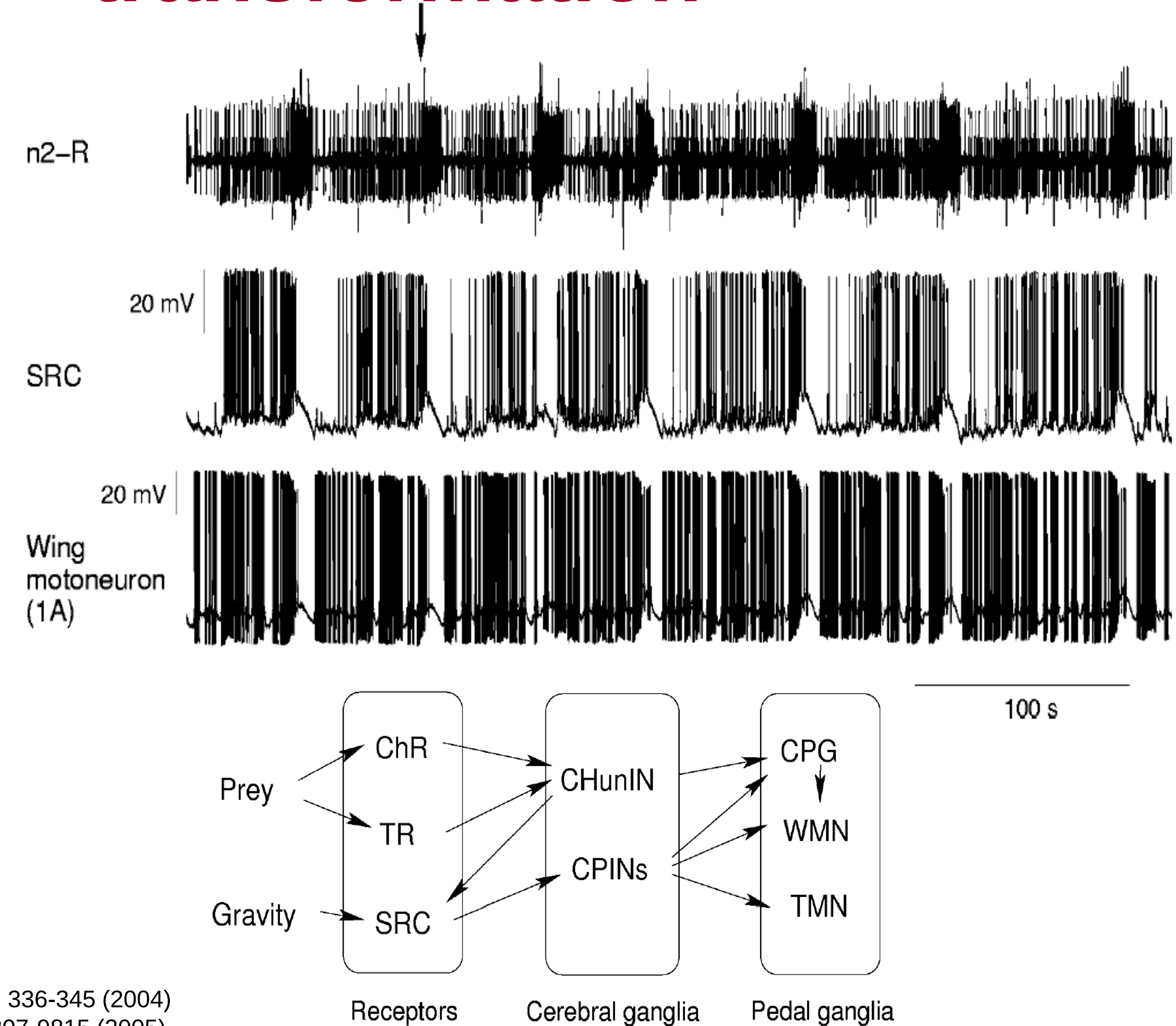
Hunting Behavior

The preferred head-up position is controlled by a pair of statocysts



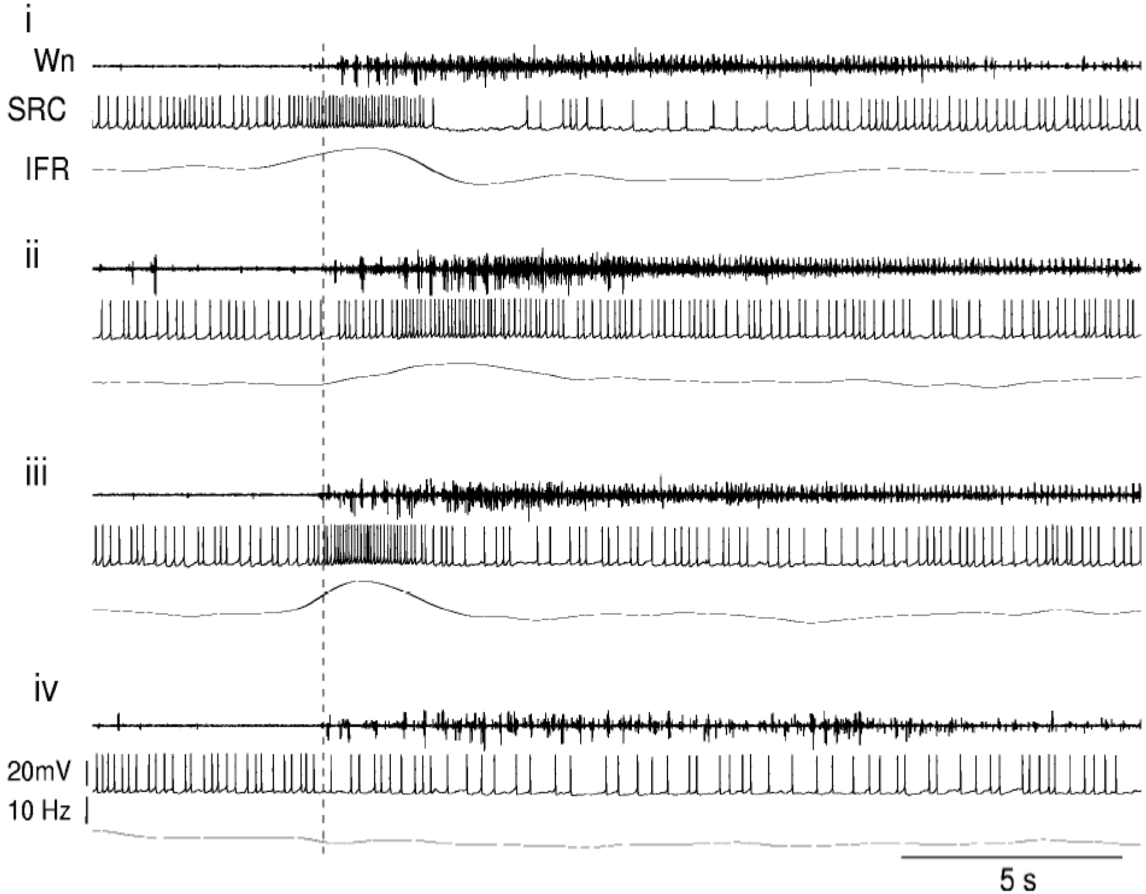
Prey: *Limacina helicina*

Clione's sensory-motor transformation



Levi et al. *Journal of Neurophysiology* 91: 336-345 (2004)
Levi et al. *Journal of Neuroscience* 25: 9807-9815 (2005)

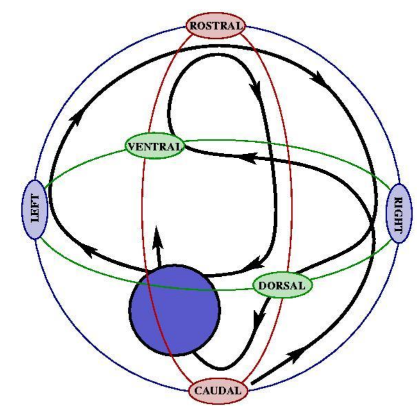
Clione's activity during fictive hunting

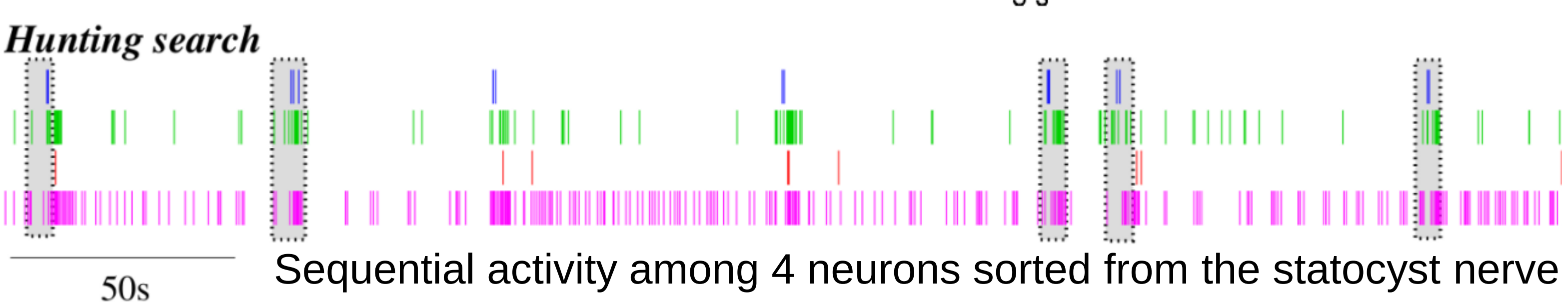


Levi et al. *Journal of Neurophysiology* 91: 336-345 (2004)

Levi et al*. Journal of Neuroscience* 25: 9807-9815 (2005)

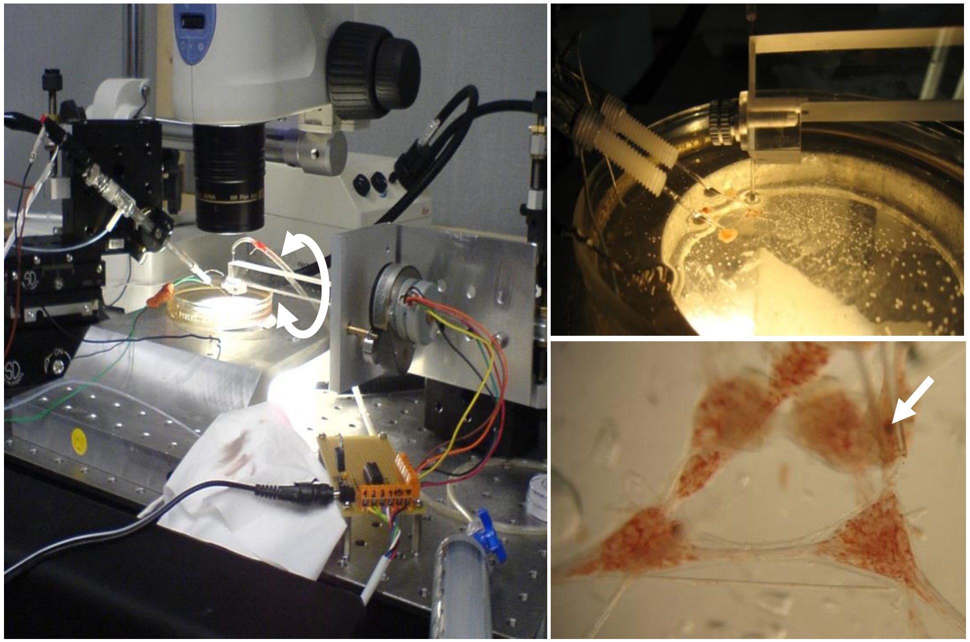
Latorre et al. *PLoS Computational Biology 9(2) : e1002908* (2013)

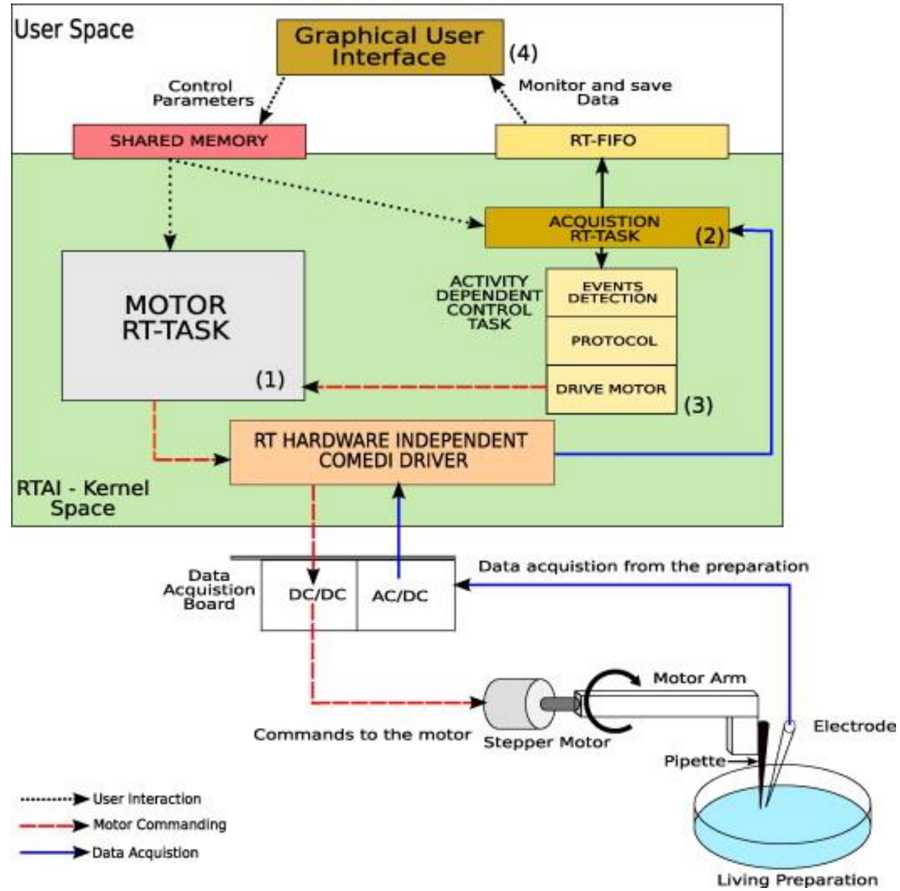




Sequential activity among 4 neurons sorted from the statocyst nerve

Sensorymotor transformation: activity-dependent mechanical stimulation





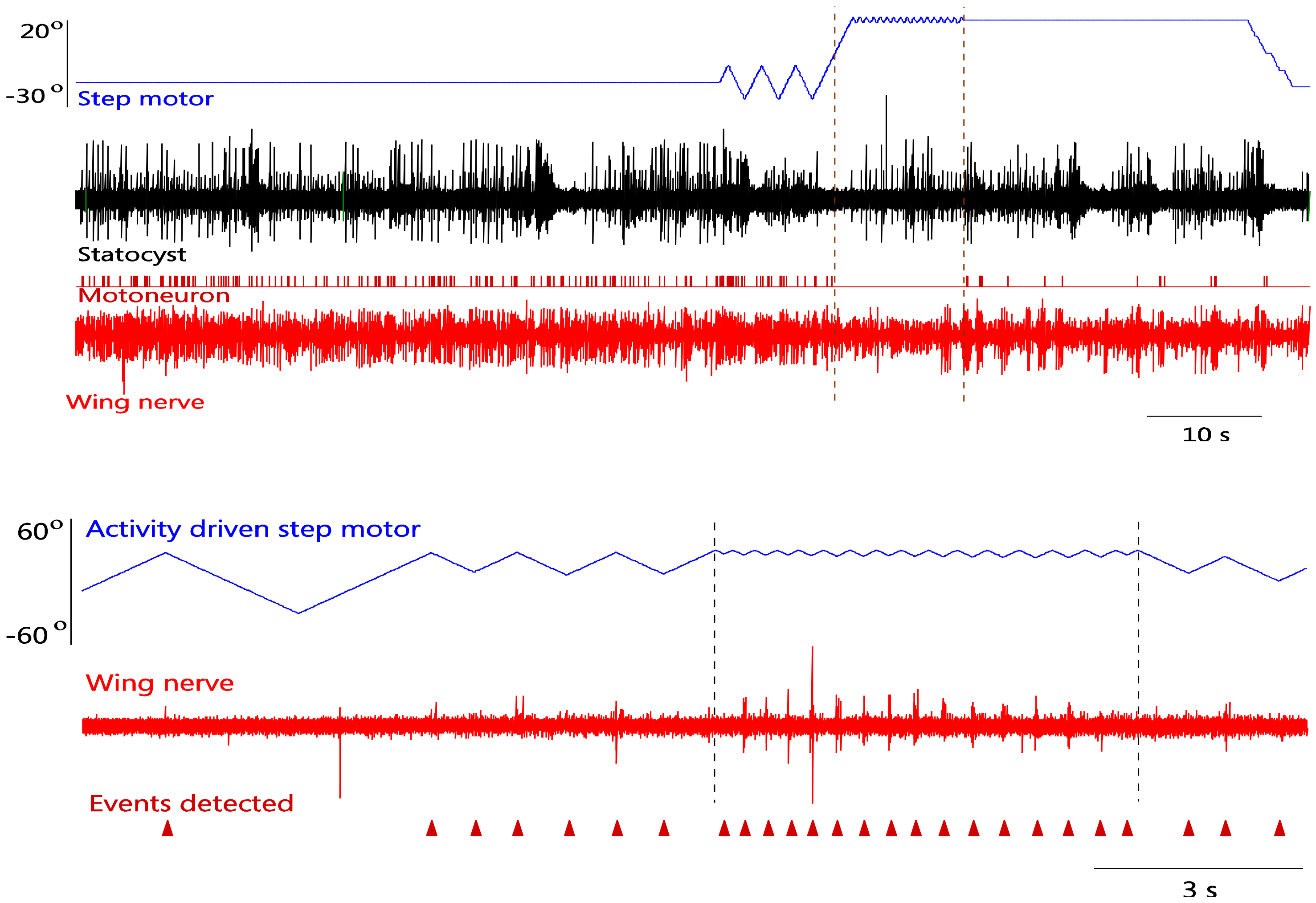
Setup:

- Stacotyst gently sucked at the tip of a micropipette
- Micropipette at the end of an arm moved by a step motor
- Electrodes at stages of the sensorymotor transformation
- Step motor controlled by the RTDO driven by events detected in the recordings

Muniz et al. *Journal of Neuroscience Methods* 172: 105-111 (2008)

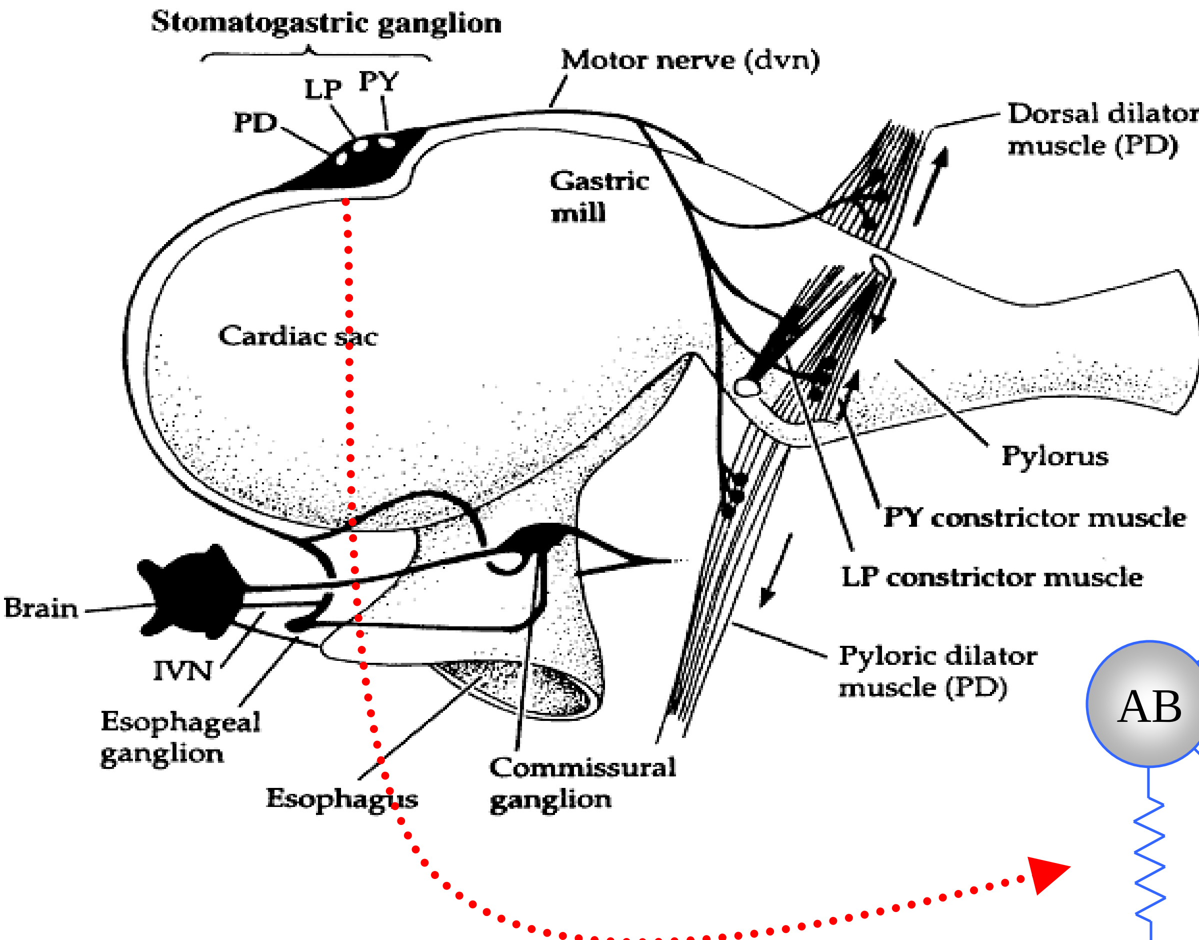
Chamorro et al. *PLoS ONE* 7(7): e40887 (2012)

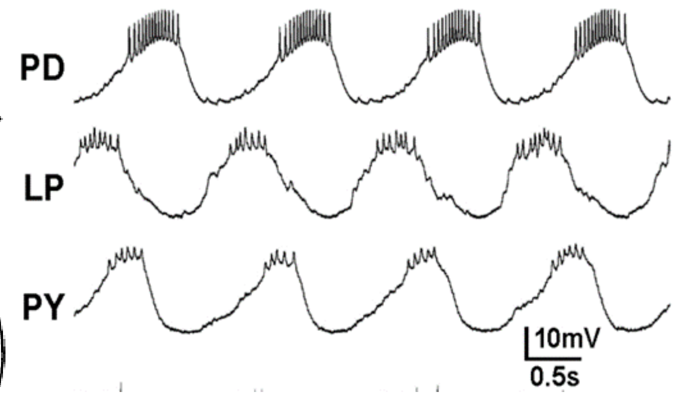
Activity dependent mechanical stimulation: Receptive field automatic search



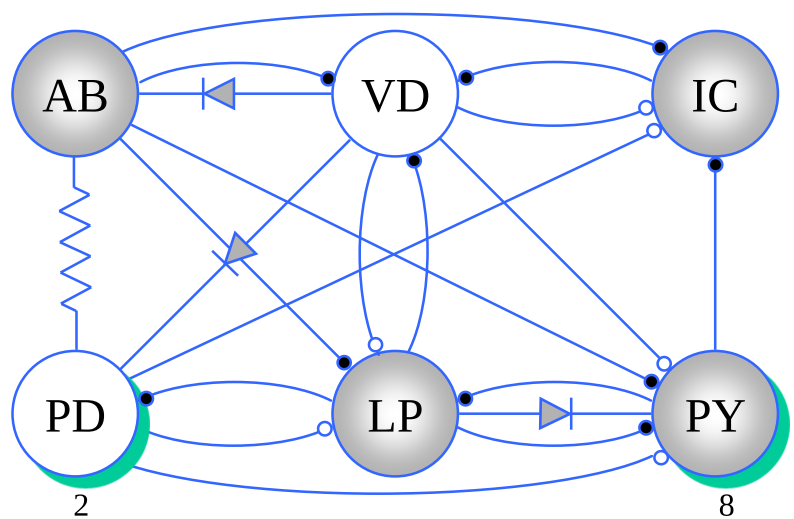
Muniz et al. *Journal of Neuroscience Methods* 172: 105-111 (2008). Chamorro et al. *PLoS ONE* 7(7): e40887 (2012)

Sequential activity in CPGs





Pyloric CPG: 14 neurons

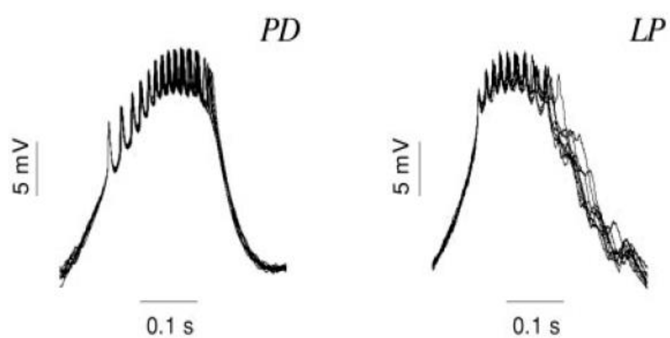


Non-open topology: every member of the circuit receives at least one connection from another member of the CPG

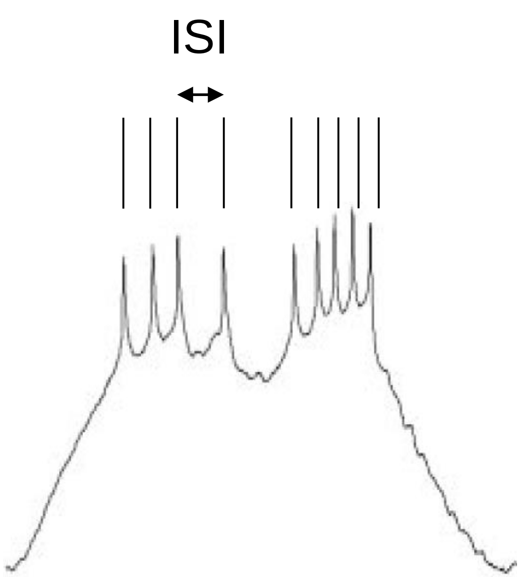
Neural Signatures

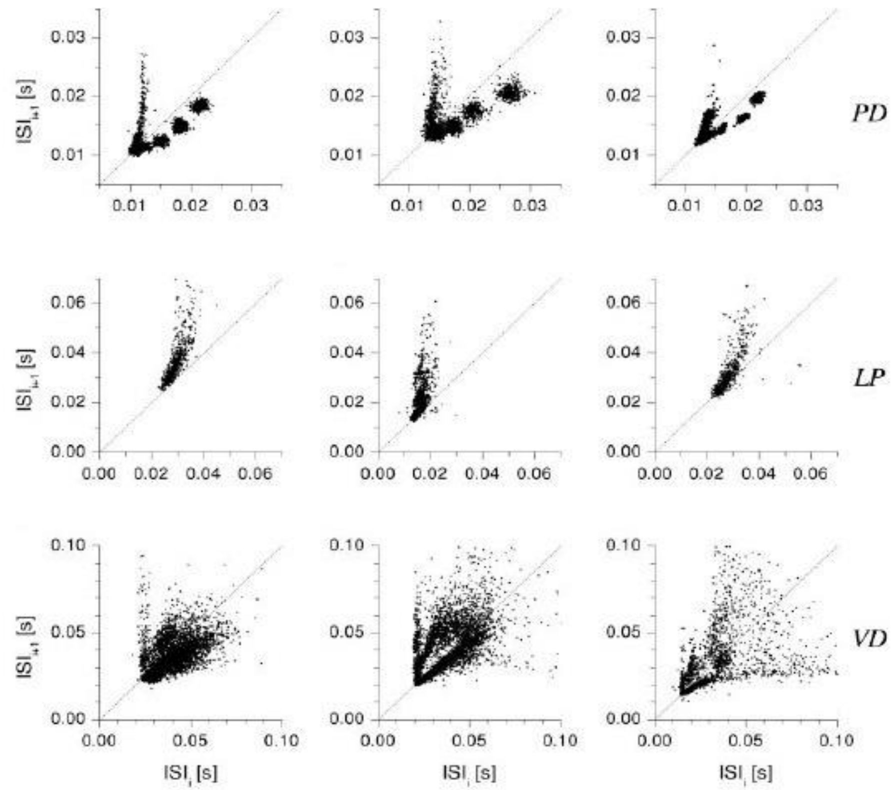
A neural signature is a reproducible *cell-specific, intraburst interspike interval distribution*

Szücs et al. 2003, *J. Neurophysiol.* 89: 1363



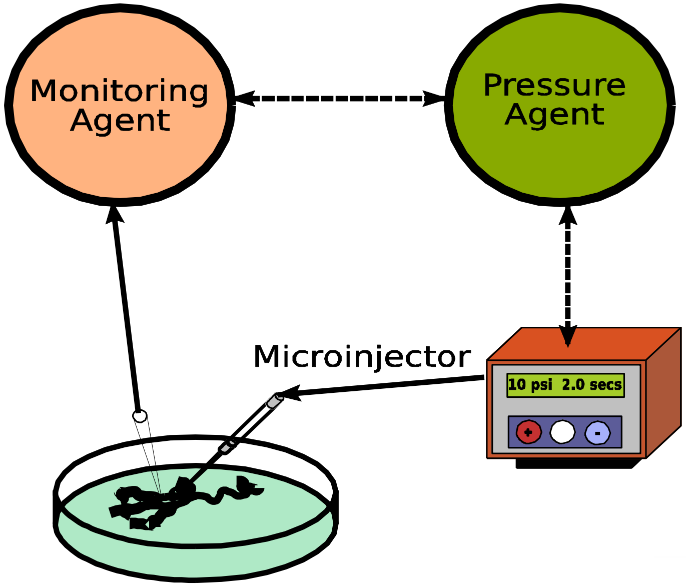
Ten traces of consecutive bursts

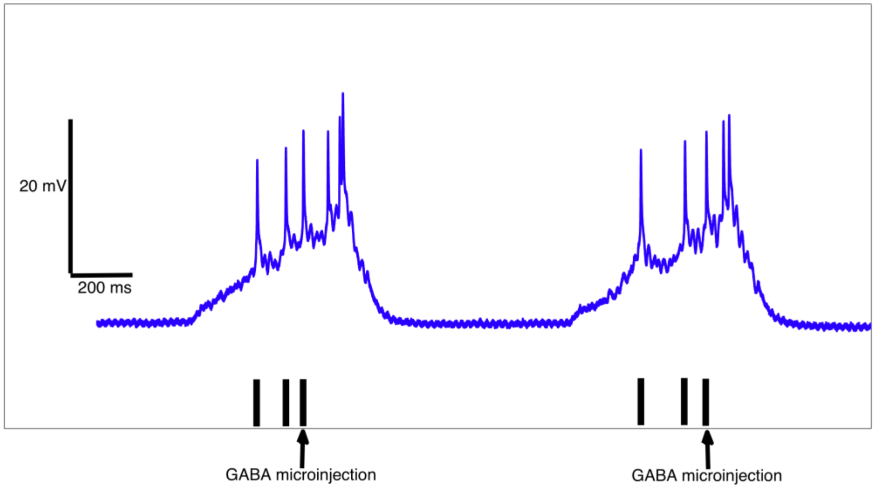




Signatures of PD, LP and VD pyloric neurons from **3 different animals**

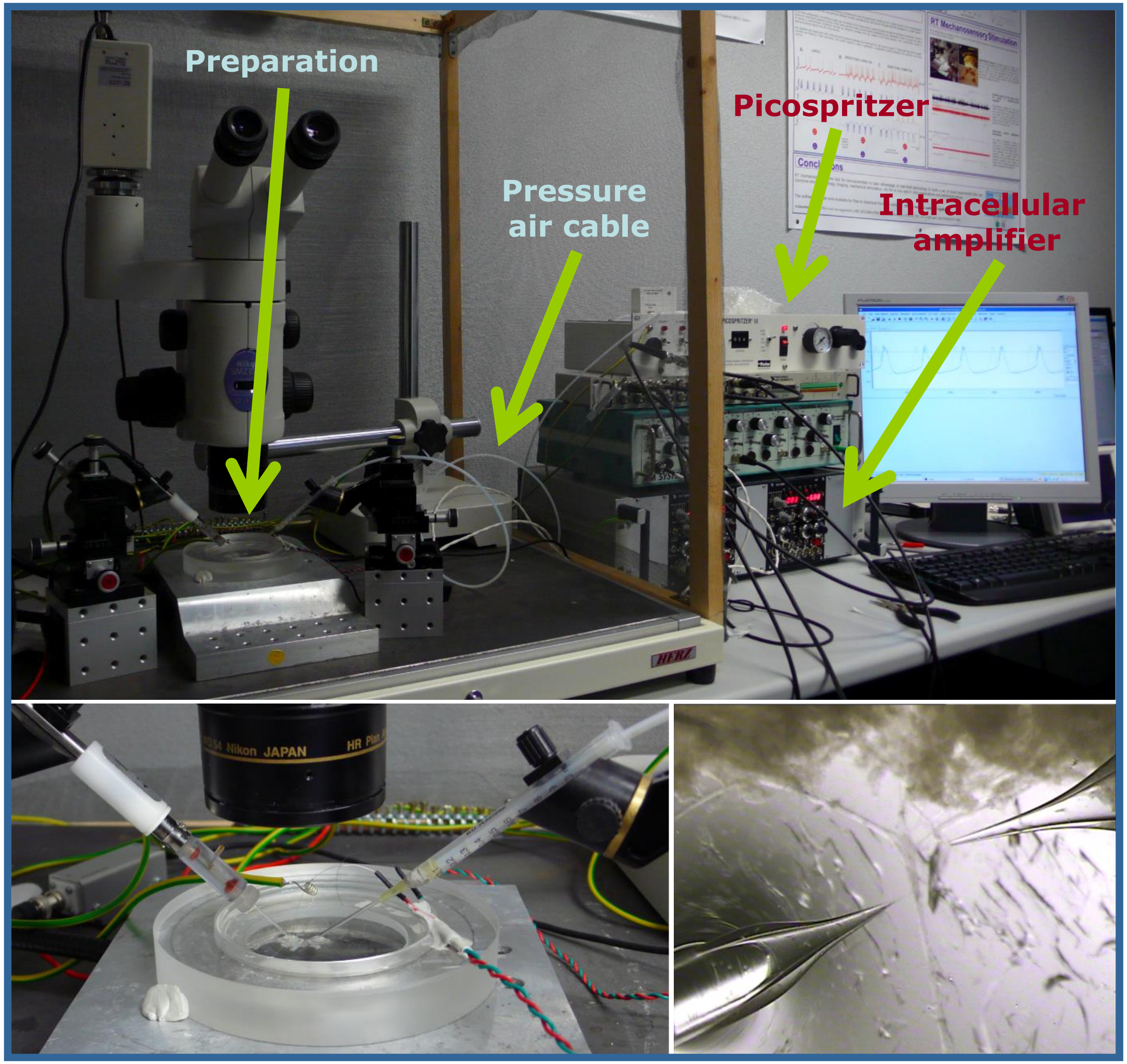
Activity-dependent neurotransmiter microinjection



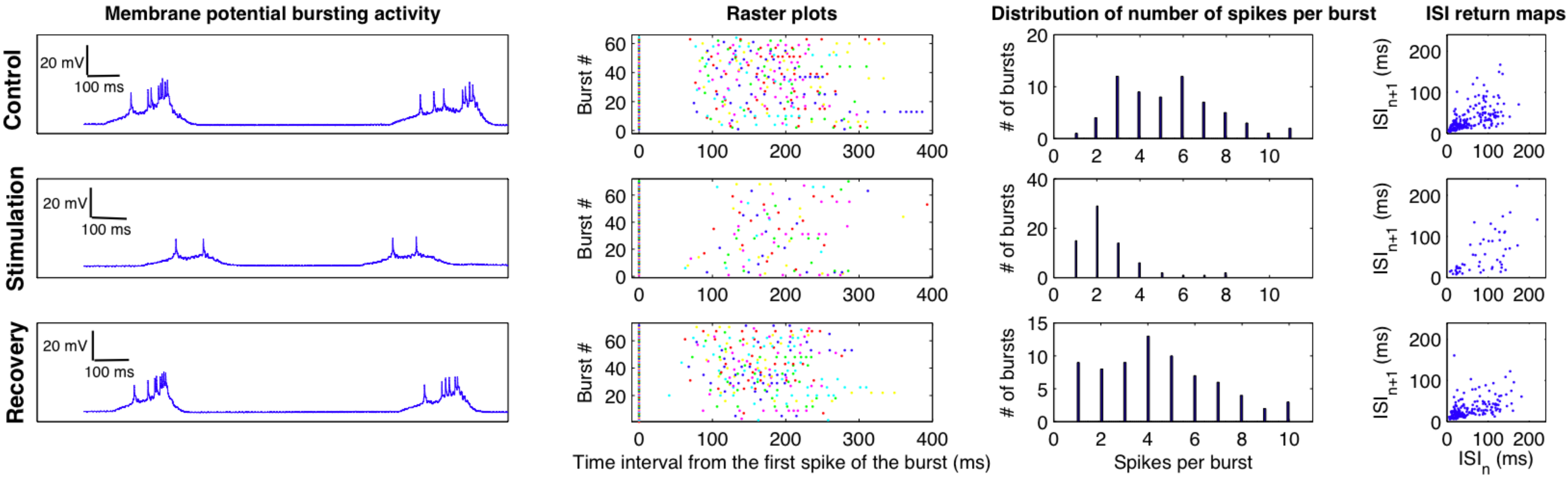


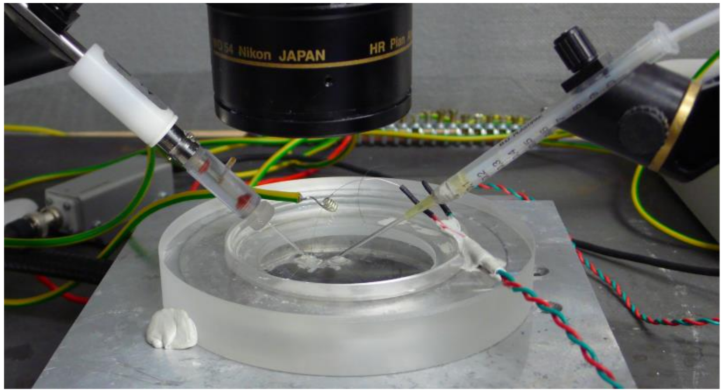
The membrane potential of a neuron is measured and an activity-dependent stimulation protocol of GABA microinjection is implemented with an RTDO. The duration of the micro-injections and the stimulation precise instant are controlled through the activity-dependent protocol.

Experimental setup



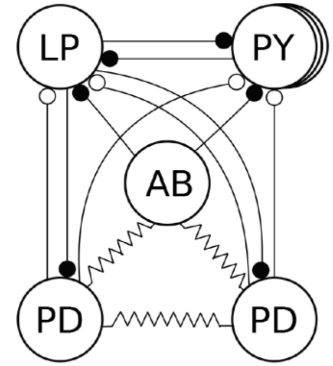
Example of the effect of the activity-dependent GABA microinjection



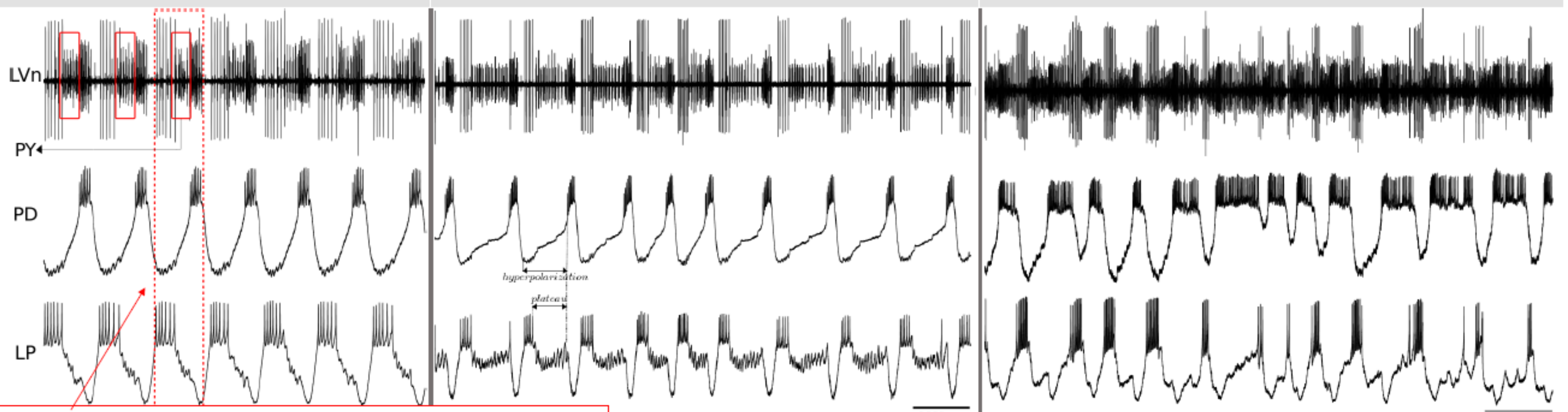


Chamorro et al. *BMC Neuroscience* 10: P296 (2009)

Regular and non-regular sequential activations



Regular Control	Irregular Control	Ethanol
• Constant PD burst duration • Constant LP burst duration • Constant hyperpolarization	• Constant PD burst duration • Higher variability in LP burst duration • LP presents larger plateau • Irregular hyperpolarization	• Flexible and very long PD burst duration • Restricted LP spike burst duration • Irregular hyperpolarization

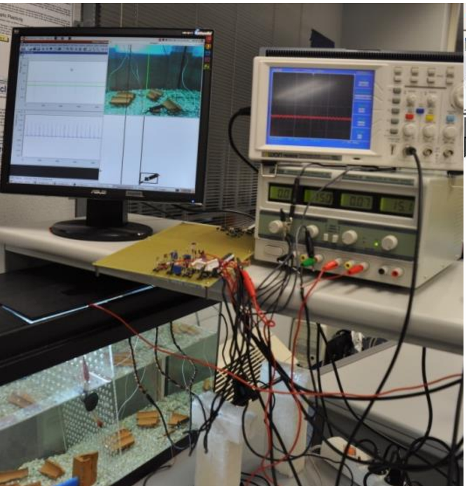


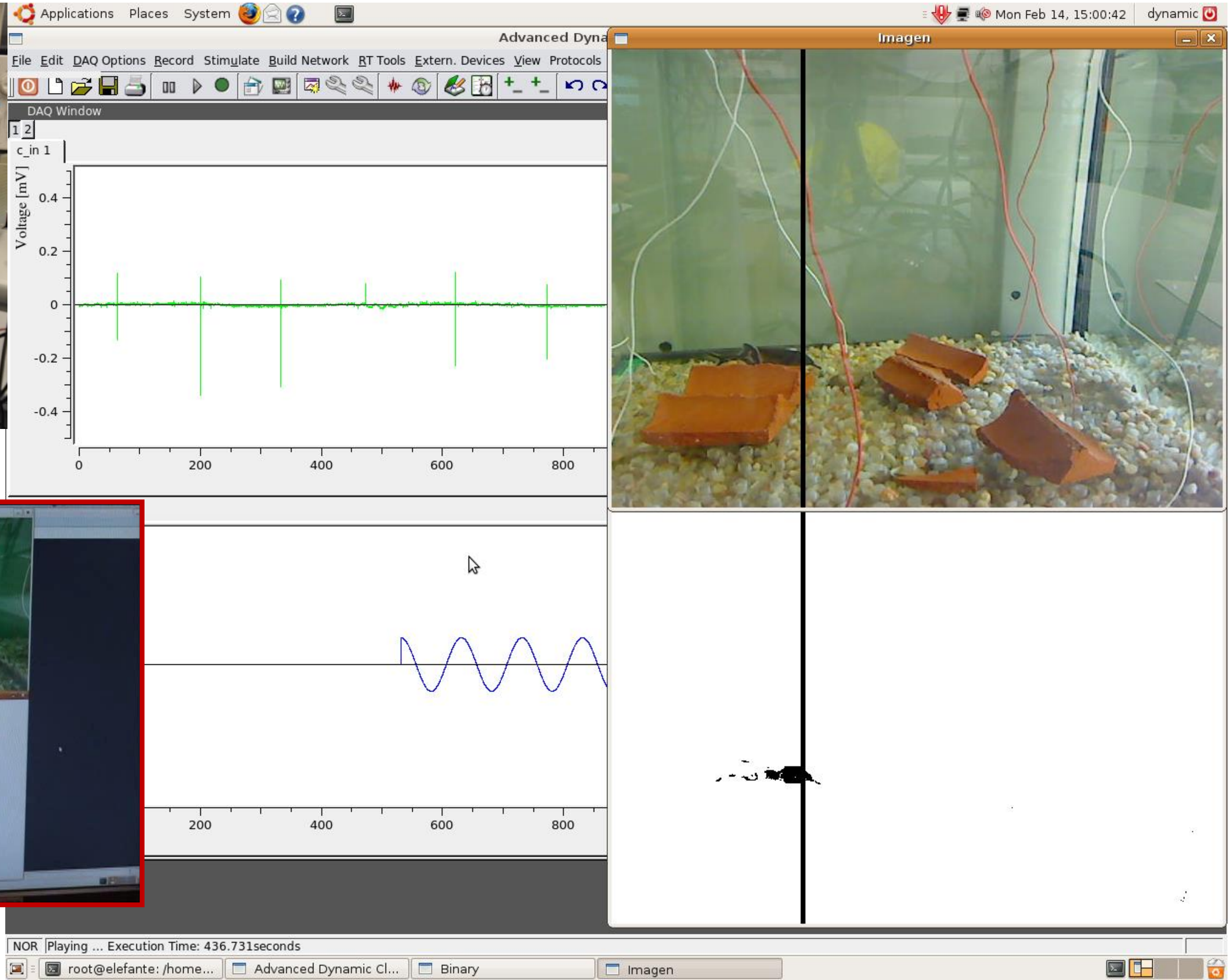
Triphasic rhtythm LP-PYs-PDs order

Carcinus maenas

Elices et al, *Scientific Reports* 2019

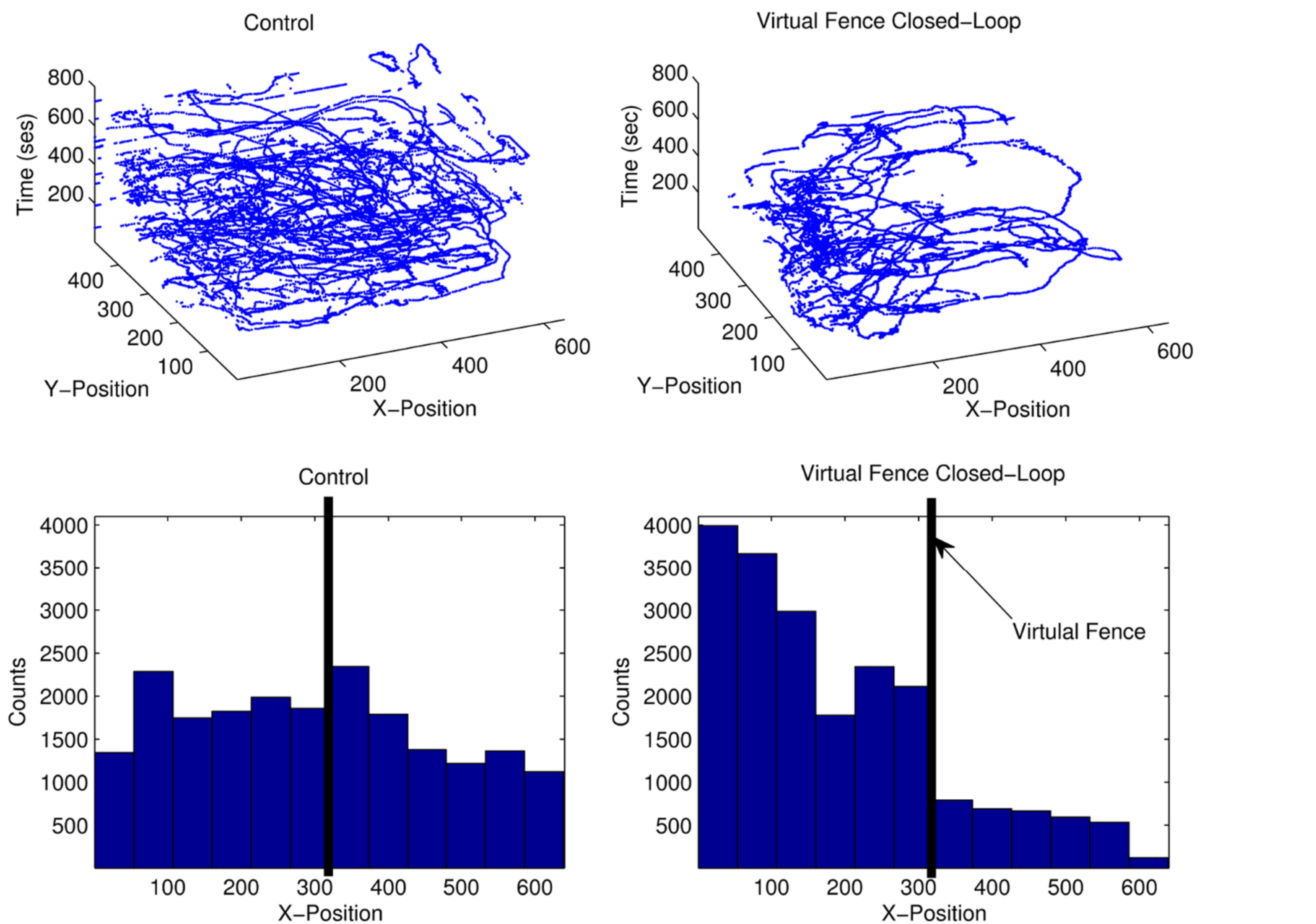
Activity-dependent stimulation with online video tracking in weakly electric fish





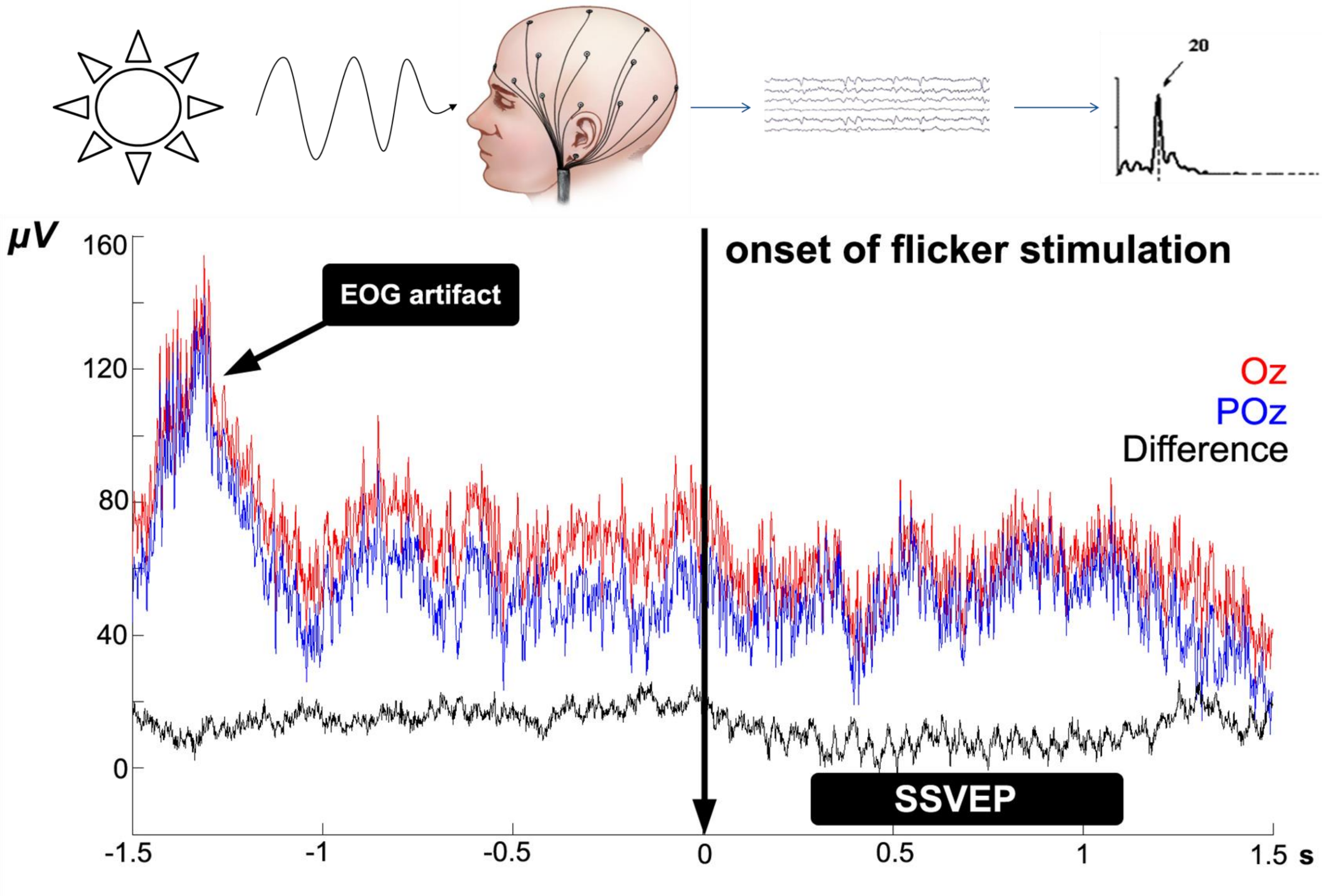
Elephantnose fish
Gnathonemus petersii

Virtual fence for electric fish

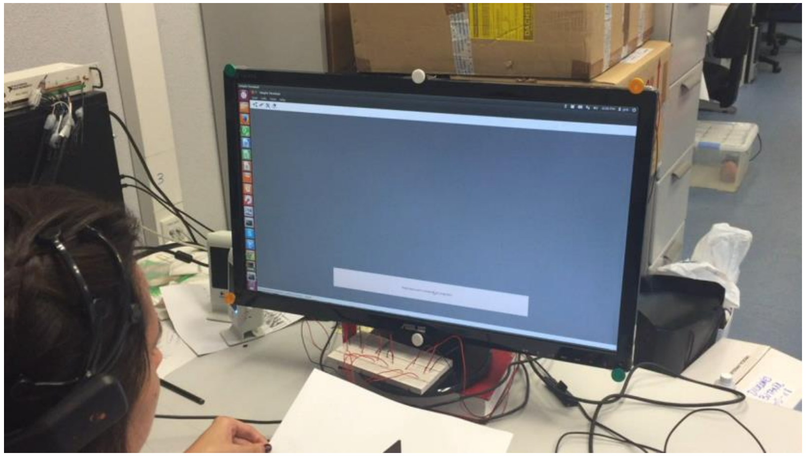


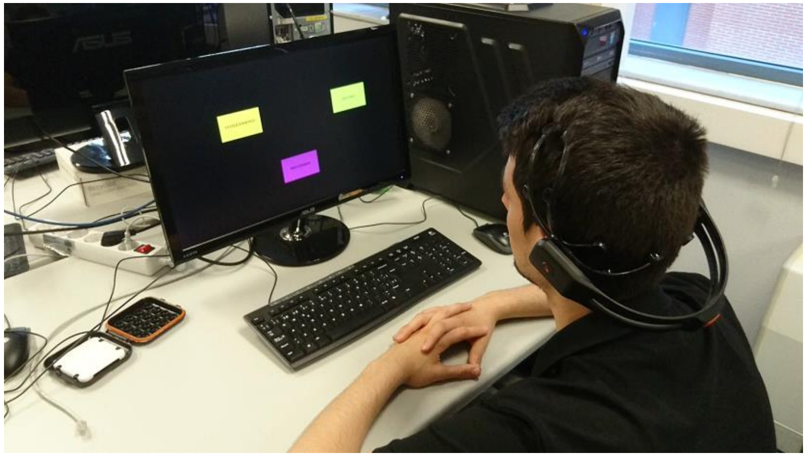
Chamorro et al. *PLoS ONE* 7(7): e40887 (2012)

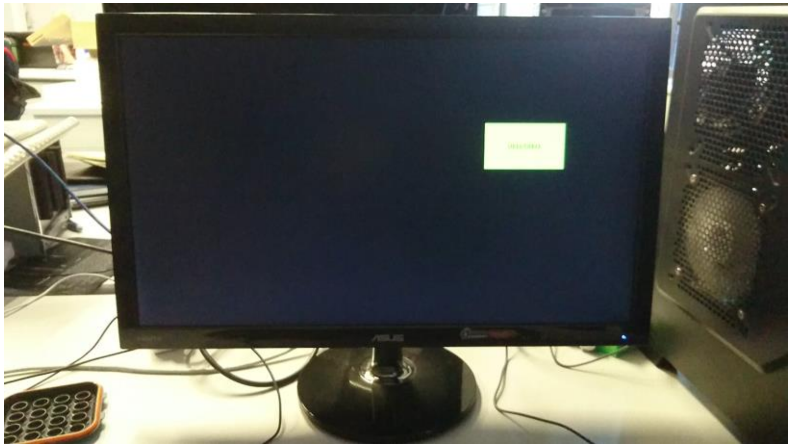
BCIs based on visually evoked potentials



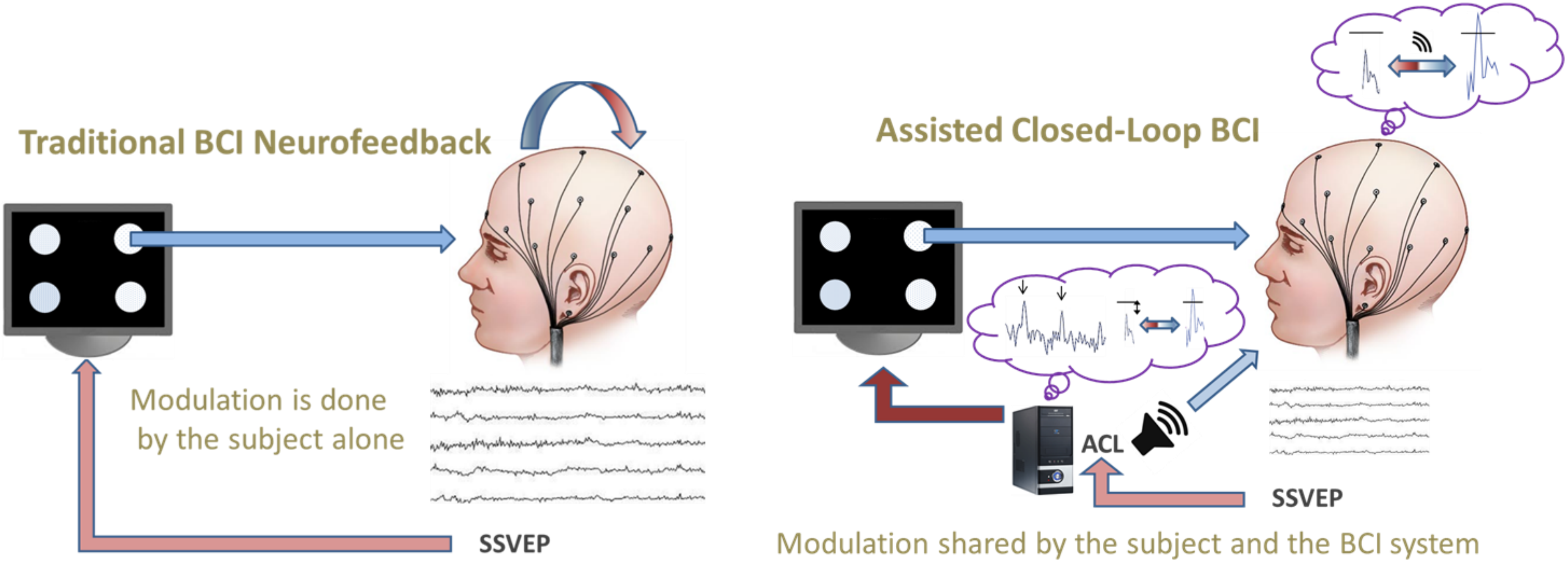
Highly adaptable and personalized SSVEP-based BCIs







Traditional vs Assisted Closed-loop BCIs



Personalized selection of the best set of compatible stimulation frequencies

J. Fernandez-Vargas, H.U. Pfaff, F.B. Rodriguez, P. Varona. Assisted closed-loop optimization of SSVEP-BCI efficiency. *Frontiers in Neural Circuits* 7: 27 (2013).

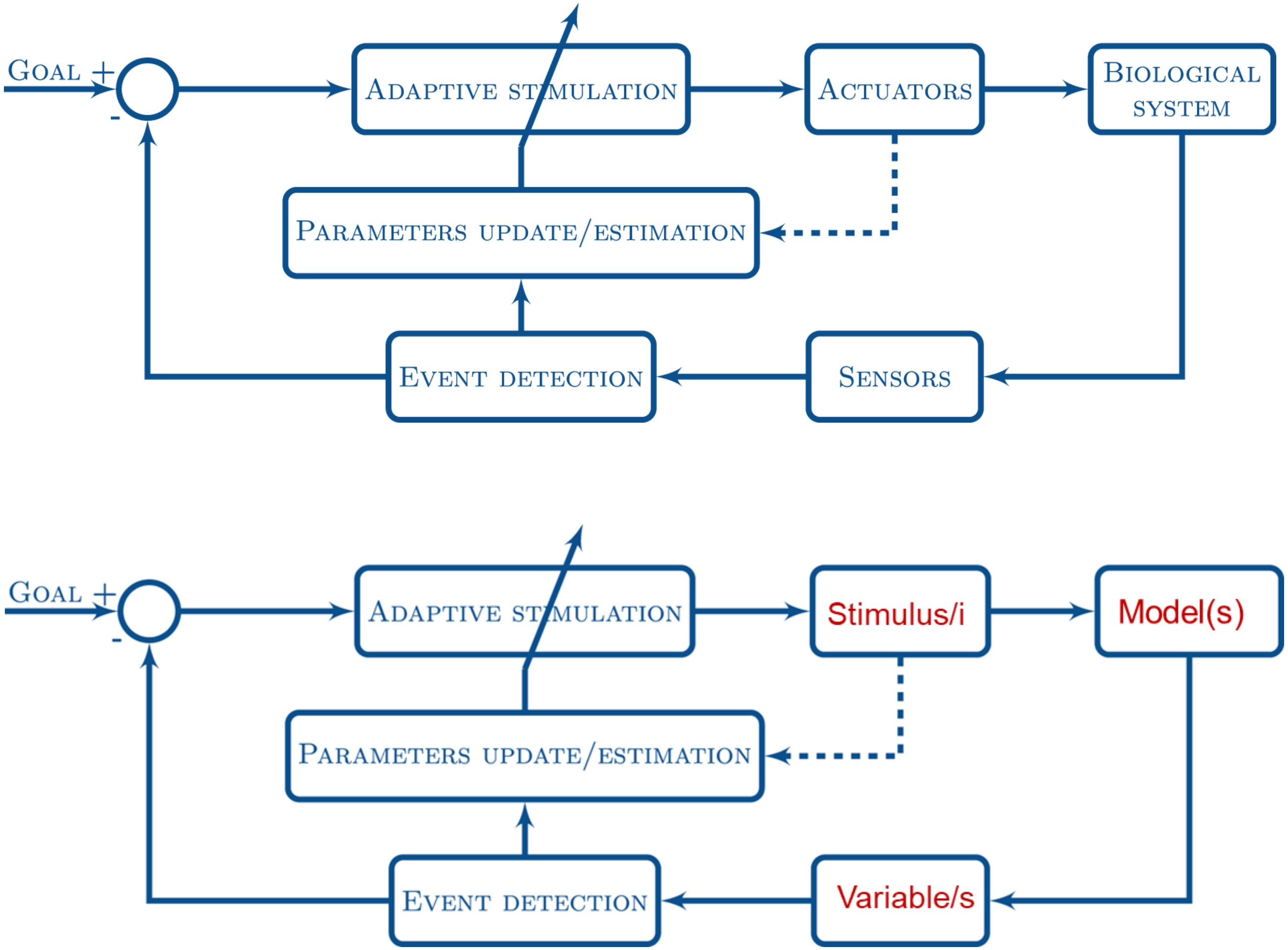
D. Rodríguez-Muñoz et al. Frequency and phase personalized SSVEP BCIs, in preparation.

Results- Experiments with N=18 subjects

Fernandez-Vargas et al. *Frontiers in Neural Circuits* 7: 27 (2013)

	ITR Pre	ITR Top	ITR Mean ACL	ITR Mdn ACL	ITR Max ACL
	.24	21.19	15.01	15.34	21.57
	5.65	7.34	5.03	3.06	11.7
	11.88	.82	15.25	19.48	26.33
	17.89	27.29	26.62	29.21	34.9
	16.9	7.09	12.08	8.42	12.98
	0	0	.56	0	6.98
	19.32	11.68	21.18	18.58	36.92
	0	1.88	5.12	5.12	10.56
	6.76	1.79	9.17	9.17	12.47
	16.53	16.18	21.16	22.31	30.02
	5.35	18.23	21.84	22.16	31.47
	0	0	4.67	9.42	9.73
	10.07	19.32	18.06	18.06	28.32
	12.7	16.53	11.13	12.7	16.18
	.21	.22	5.4	4.96	9.57
	0	3.43	6.34	4.42	21.14
	0	0	.42	.42	.76
	3.43	12.98	15.43	14.63	18.58
Median	**5.5**	**7.22**	**11.61**	**11.06**	**17.38**

Models can also go closed loop



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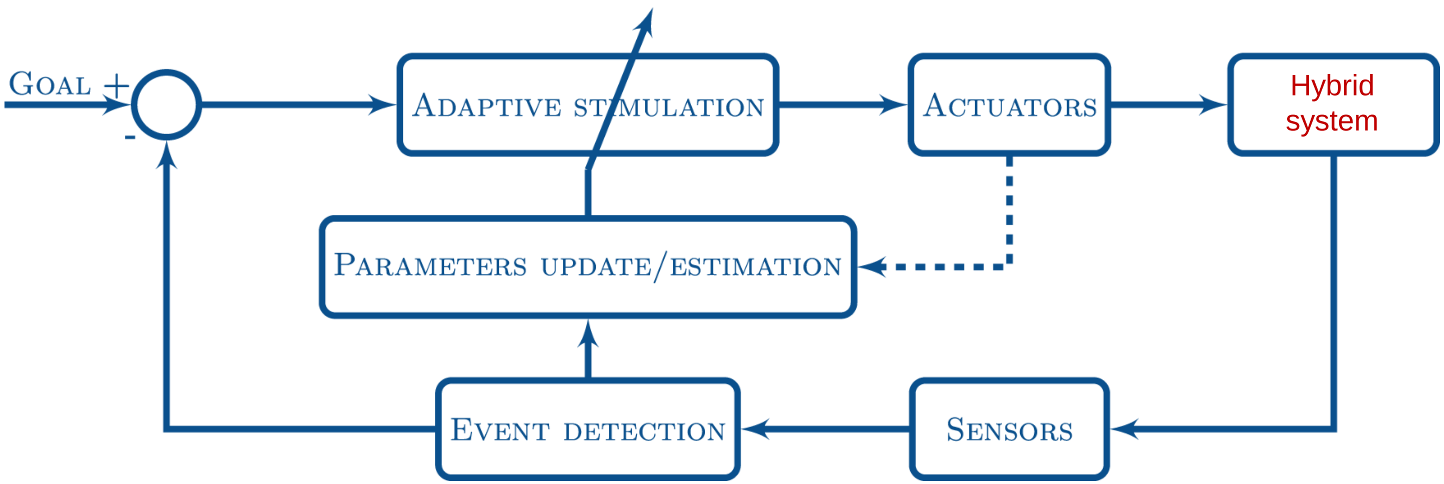
and also hybrid circuits



M. Reyes-Sanchez, R. Amaducci, I. Elices, F.B. Rodriguez, P. Varona. 2020. Automatic adaptation of model neurons and connections to build hybrid circuits with living networks. *Neuroinformatics* 18: 377–393.

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SUMMARY:

Model driven activity-dependent stimulation and closed-loop technologies can be used to:

- Reveal information processing in neural dynamics, particularly transients.
- Assess control of natural and pathological states.
- Bridge between disparate levels of analysis.
- Automate experiments.
- Relate specific dynamics to information processing and behavior.
- A new generation of personalized and highly adaptive BCIs.

Thank you!

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Further reading:

- M. Reyes-Sanchez, R. Amaducci, I. Elices, F.B. Rodriguez, P. Varona. 2020. Automatic adaptation of model neurons and connections to build hybrid circuits with living networks. *Neuroinformatics* 18: 377–393.
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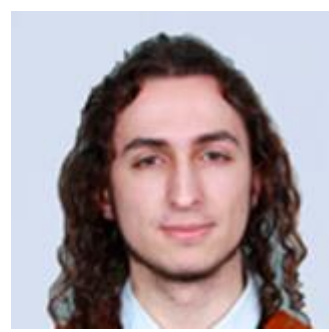

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