Computational Neuroscience Unit (FY 2019 Staff Profiles)

FY2015 Annual Report

Computational Neuroscience Unit

Professor Erik De Schutter

Abstract

We use computational, data-driven methods to study how neurons and microcircuits in the brain generate rhythmic activity. We are interested in how fundamental properties of cell as a neuron (ion channels and its morphology) interact with one another during common neural functions like information processing or learning. Most of our models concern the cerebellum as the brain structure has a relatively simple anatomy and the physiology is the most neurons has been studied extensively, allowing for detailed modeling of many different levels of complexity.

1. Staff

Professor Erik De Schutter

- Ian Hepburn, Technical Staff
- Andrew Gilchrist, Technical Staff (from May 2015)
- Hirosanna Gangan, Technical Staff (till June 2015)
- Sridhar Raghavachari, Staff Scientist
- Christina Ziburkus, Research Intern (July 2016)

Cellular modeling

- Sungho Hong, Group Leader
- Anna Tatsenko, Researcher (till February 2016)
- Yuichi Murayama, Researcher

Network modeling

- Benjamin Torben-Nielsen, Group Leader (till October 2015)
- Tom Close, Research Intern (till June 2015)
- Sergio Verduzco, Researcher (from October 2015)
- Ankur Sinha, Research Intern, Special Research Student (till December 2015)

Software development

- Weiliang Chen, Researcher
- Dustin Wittenber, Researcher (from July 2015)

Visiting Researcher

- Mikaella Fouchara (from January 2016)

Research Interns

- Jonathan Jarvis, Research Intern (till June 2015)
- Chiara Nutarelli, Research Intern (till April 2015)
- Ankur Gupta, Research Intern (from September 2015)

Rotation Students

- Sergey Zolotov, Student (Term)
- Ankur Gupta, Student (Term)

Research Unit Administrator

- Sachie Nakazato

2. Collaborations

- **Finance: Cerebellum physiology, multiple themes**
  - Type of collaboration: Joint collaboration and graduate program
  - Researchers:
    - Professor M. Gugliano, University of Antwerp, Belgium
    - Professor D. Sciatto, University of Antwerp, Belgium
    - Professor Jan Germuska, Charles University
    - D. Rudolowski, University of Antwerp, Belgium
- **Theme: Spiking activity of monkey cerebellar neurons**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor H.P. Thier, University of Tübingen, Germany
    - Professor Wolfgang Maier, University of Tübingen, Germany
    - Dr. M. Junker, University of Tübingen, Germany
    - A. Schöngutz, University of Tübingen, Germany
- **Theme: Human Brain Project simulation development**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Prof. P. Schwerdt, Ecole Polytechnique Fédérale de Lausanne, Switzerland
    - F. Delacretaz, Ecole Polytechnique Fédérale de Lausanne, Switzerland
- **Theme: Molecular identification of cerebellar signaling pathways and cerebellar synaptomics**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor E. Sezaki, Korea Institute for Science and Technology (KIST), Korea
- **Theme: Modeling of effects of ethanol on the cerebellum**
  - Type of collaboration: Joint research
  - Researchers:
    - Professor C.F. Valenzuela, University of New Mexico, United States of America
- **Theme: In vivo cerebellar activity**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor C. De Zeeuw, Erasmus Medical Center, Rotterdam, The Netherlands
    - Dr. Chris I. De Zeeuw, Erasmus Medical Center, Rotterdam, The Netherlands
    - A.M. Negrello, Erasmus Medical Center, Rotterdam, The Netherlands
- **Theme: Purkinje cell morphology and physiology, modeling**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor M. Häusser, University College London, United Kingdom
    - Professor A. Roth, University College London, United Kingdom
    - Dr. S. Dieudonne, Ecole Normale Supérieure, Paris, France

3. Activities and Findings

Cellular mechanisms regulating firing and synaptic properties of neurons

Leak currents in Purkinje cells are non-linear

In their seminal work on squid giant axons, Hodgkin, and Huxley approximated the membrane leak current as Ohmic, i.e., linear, since in their preparation, sodium and potassium contributed due to the influence of ionic concentration on reversal potential. Most studies on mammalian neurons have followed this approach. However, in Purkinje cells, the leak current has been shown to be non-linear, with both inward and outward rectification and input resistance of mammalian neurons (when other major voltage-sensitive and ligand-gated ionic currents are blocked) has been found to increase with membrane voltage, following the prediction of a Goldman-Hodgkin-Katz (GHK) based passive membrane model (Huang et al., 2015). However, the underlying ionic mechanism for such non-linear leak current remains unknown. Our preliminary results show that the non-linear leak current in Purkinje cells is not due to voltage-gated potassium channels since the leak current persists when voltage-gated potassium channels are blocked. Further, the leak current persists when Purkinje cells are dialyzed with Cesium-based internal solution, which should block most of the potassium channels. Finally, the leak current persists when extracellular sodium is replaced with NMDG, a non-permeant cation, suggesting that the leak current is not carried by sodium ions. These results suggest that the non-linear leak current in Purkinje neurons is not due to voltage-gated potassium channels, but may be due to other ion channels or other mechanisms. We are currently testing the effects of cesium, TEA, 4-AP, and Barium on the leak current to further dissect the underlying ionic mechanism.

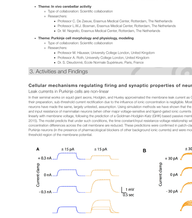

Figure 1. A. Comparison between voltage responses of a passive Ohmic model (blue traces) and a GHK model (orange traces) to +/−13 pA (solid lines) and −13 pA (inverted and superimposed, dotted lines) current injections for 2 seconds, at three different holding currents (−70 mV, −80 mV, and −90 mV). The Ohmic model (with a leak conductance of 2 nS) shows a linear response to current injection, which is clearly inverted, nevertheless the response to positive and negative currents overlap for both conditions. **B.** Similar plot as in A, but for a Purkinje cell when all major ionic currents blocked, stimulus delivered at three different holding potentials (−70, −80 and −90 mV for bottom to top).

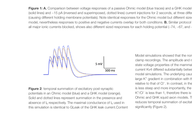

Figure 2. Temporal summation of excitatory postsynaptic potentials (EPSPs) in a Purkinje cell model (black and gray) with (orange traces) and without (blue traces) Ohmic leak conductance. Stimulus consisted of 100 EPSPs (at 1 ms interval) with a Poisson distribution. Model cells were held at −70 mV. Ohmic leak conductance was set at 2 nS. Note that the amplitude of the EPSPs in the Ohmic model cell are much smaller than those in the non-Ohmic model cell, and the amplitude of the EPSPs in the Ohmic model cell reaches a steady state after 50 EPSPs, while the amplitude of the EPSPs in the non-Ohmic model cell continues to increase even after 100 EPSPs. The amplitude of the EPSPs in the non-Ohmic model cell reaches a steady state after about 100 EPSPs.

Model simulations showed that the non-linear leak affects voltage-dependent dendritic integration. We found that the non-linear leak affects several properties of the membrane including input resistance (which increases with hyperpolarization), resting potential (which becomes more hyperpolarized), and the amplitude of the excitatory postsynaptic potentials (EPSPs) elicited by a fixed number of synaptic inputs (which increases with hyperpolarization). In the equal axon, the 1st EPSP elicited in the Ohmic model cell is larger than that in the non-Ohmic model cell, but the amplitude of the EPSPs in the Ohmic model cell reaches a steady state after about 50 EPSPs, while the amplitude of the EPSPs in the non-Ohmic model cell continues to increase even after 100 EPSPs. In contrast, in the equal axon, the 1st EPSP elicited in the Ohmic model cell is smaller than that in the non-Ohmic model cell, but the amplitude of the EPSPs in the Ohmic model cell reaches a steady state after about 100 EPSPs, while the amplitude of the EPSPs in the non-Ohmic model cell continues to increase even after 100 EPSPs. These results show that the non-linear leak current in Purkinje cells affects dendritic integration of synaptic inputs.

Together, our results demonstrate the importance of more mechanistic ion channel conductances in defining the functional properties of the passive membrane in mammalian neurons as well as other excitable cells.

Duration of Purkinje cell complex spikes increases with their firing frequency

Climbing fiber triggered complex spikes are massive depolarization bursts of the cerebellar Purkinje cell, showing several high frequency spikelets followed by a long-lasting slow depolarization. Climbing fiber activity has been shown to be tightly coupled to the ongoing motor behavior, and perturbations, sensitively recorded in awake primates performing saccadic tasks (Yang et al., 2014). Even Purkinje cell simple spikes exhibit a range of complex spike shapes with profoundly different duration and number of spikelets. The initial part of the complex spike was rather constant but the tail part differed greatly, with a pronounced tail in the last spikelets causing a large variation in the duration of complex spikes.

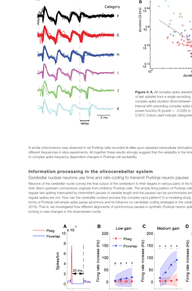

Figure 4. A. All complex spike waveforms that offered only a deep tail were pooled from a single recording. **B.** Distribution of the complex spike duration (time between first and last spikelet) across different cells (ordered by median duration). **C.** Coefficient of variation (CV) of the power-function fit (power = −1.5) versus the tail skew (left: $R^2 = 0.8$, $p < 0.001$). Colors used indicate categories.

A similar phenomenon was observed in rat Purkinje cells recorded in either spon-taneous extracellular stimulation of climbing fibers at different frequencies. An experiment that recorded simple spikes showed that simple spike firing rate increases that cause hyperpolarization (Figure 5). Pause lengthening synchronized postsynaptic inhibition evoked by molecular layer stimuli (see Figure 6).

Information processing in the olivocerebellar system

Cerebellar nuclear neurons can fire and code information during synchronized Purkinje neuron pauses

Neurons of the cerebellar nuclei convey the final output of the cerebellum to their targets in various parts of the brain. Within the cerebellum they receive inhibitory input from Purkinje cells and excitatory input from mossy fibers and climbing fibers. Purkinje cells have been shown to regular fast firing and exhibit long-lasting intermittent pauses of variable length and duration. Cerebellar nuclear neurons have been shown to regular spikes and not. How can the cerebellar nucleus process this complex input pattern? In a modeling study, we investigated different ways in which the cerebellar nucleus could process the input from Purkinje cells. We found that the cerebellar nucleus can process the input from Purkinje cells. That is, we investigated how different alignments of synchronous pauses in synthetic Purkinje spike trains affect other firing-locking or rate changes in the downstream neuron.

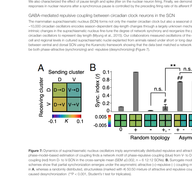

Figure 5. In all panels red rasters stands for pauses beginning synchronous (from the same cycle) and black rasters for asynchronous shifted signals. **A** Population spike firing histogram of all Purkinje cells projecting on the cerebellar nucleus neuron cluster. One cycle histogram synchronous pause of 20 ms for both cases of synchronisation. **B** Mean and standard deviation of firing rate of cerebellar nucleus neuron response quantified for both conditions and for low input gain. **C** Same for medium input gain. **D** Same for high input gain. (1 repeated simulations. Error bar of panel C and D are smaller than the line width.)

We found that Purkinje neuron synchrony is mainly responsible for changes in the firing rates of cerebellar nucleus neurons. Pause lengthening synchronized postsynaptic inhibition evoked by molecular layer stimuli (see Figure 6). Pause lengthening synchronized postsynaptic inhibition could not be distinguished from each other. Pause lengthening synchronization-mediated greater firing rate increases that cause hyperpolarization (Figure 5). Pause lengthening synchronized postsynaptic inhibition evoking a rebound spike or nucleus rebound spike (Figure 6).

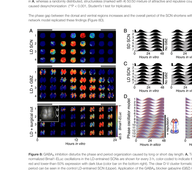

Figure 6. Variability of delay of the cerebellar nucleus neuron spike response after a pause calculated from 100 repeated simulations for each pause (weakening hyper-synchronisation). Same cluster organisation and connectivity as Figure 5.

We also characterized the effect of pause length and spike jitter on the nuclear neuron firing. Ideally, we demonstrate that the rate of rebound responses in nuclear neurons after a synchronous pause is controlled by the preceding firing rate (or of different Purkinje cells.

GABA modulation controls coupling between cerebellar clock neurons in the SCN

The mammalian suprachiasmatic nucleus (SCN) forms not only the master circadian clock but also a seasonal clock. This neural network of approximately 20,000 neurons in each hemisphere of the brain is composed of different types of neurons. Although the SCN exhibits robust intrinsic changes in the suprachiasmatic nucleus that have the degree of network synchrony and organizes the phase relationship among circadian oscillators to represent day length (Meuryn et al., 2015). Our collaborators measured oscillations of the circle gene Bmal1, at single cell resolution in the SCN of mice and found that the phase of Bmal1 oscillation in the SCN shifted with photoperiod. The phase difference between ventral and dorsal SCN during the Kamiokande experiment suggest that this data had revealed a network that has coupling that can be both phase-advancing synchronizing and repulsive (desynchronizing (Figure 7).

Figure 8. GABA$_A$ inhibition disturbs the phase and period organization causing an almost stop-firing. **A.** Three-days-ranges of spontaneous firing rate (top) and the corresponding wavelet-transformed SCN neurons (bottom) from control (left), bicuculline (middle) and gabazine (right) treated slices. Bicuculline treatment shortened the period of spontaneous firing rate and disturbed the phase organization of the SCN network. Gabazine treatment lengthened the period (see text for details). **B.** Comparison between control and bicuculline treated slices. Bicuculline treatment significantly shortened the period in culture while keeping the cluster separation intact (see Methods). Similarly, physical separation by a surgical cut (middle) lengthened the period of spontaneous firing rate (Kim et al., 2015). Bicuculline treatment (n = 7) and physical cut (n = 6) significantly increased the phase difference and kept number of peaks through wavelet transformation using a phase-locking index (see Methods) no effect on the SCN cells (n = 6). **C.** Bicuculline treatment increased the period (P < 0.05, Student's t-test) and decreased the phase gap. **D.** The asymmetric coupling between ventral and dorsal SCN cells (n = 7) and the phase difference between ventral and dorsal SCN cells (n = 7) (P < 0.05, Student's t-test). **E.** Bicuculline treatment increased the phase difference (P < 0.01, Student's t-test) and decreased the phase gap (P < 0.01, Student's t-test). **F.** Bicuculline and the non-synaptic connections disrupted the phase organization of the SCN. The light or dark shade indicates the region of vehicle or drug application.

One of the underlying physiological mechanisms is the modulation of the intracellular chloride concentration, which can adjust the strength and polarity of the ionicmore GABA$_A$ mediated synaptic output. Increasing the strength changes the pattern of chloride transporter expression. Our results suggest that GABA$_A$ receptor-mediated synaptic output in the SCN network is critical for the generation of the circadian period and period organization but only the day length. These results indicate that the network recording of sequence time is controlled by modulation of intracellular chloride, which determines the phase relationship among and period difference between the dorsal and ventral suprachiasmatic nucleus.

4. Publications

4.1 Journals

- Ito M, Doya K (2015). The Missing Piece of the Puzzle. Neuroinformatics at the Bench. **Neuroinformatics 13**: 129-132, doi:Doi 10.1007/s12021-015-9269-3 (IF=3.01).
- De Schutter E. Stochastic effects in neuronal ion channels and cellular excitability. In Modeling the brain: from neurons to integrated neurocognitive systems. Oxford University Press, USA, 2015.
- De Schutter E. Stochastic effects of neuronal ion channels and cellular excitability. In **BMC Neuroscience**: Proceedings of the Twenty-Second Annual Computational Neuroscience Meeting: CNS*2013, Paris, France, July 13-18, 2013, pp. 1-2. Springer, 2013.
- Gallimore A R, Aimanova K G, Yoshioka M & Gallimore, R. A Computational Model for the AMPA Receptor Phosphorylation Master Switch Hypothesis of Long-Term Potentiation. **Frontiers in Neuroinformatics 9**: 24, doi:10.3389/fninf.2015.00024 (2015) (IF=3.334).
- Kaneko, G., Yoshioka, M. & De Schutter, E. Non-linear leak current affect dendritic integration of synaptic inputs. **Front Cell Neurosci 9**, 420, doi:10.3389/fncel.2015.00420 (2015).
- Minvielle, J., Bezzaoui, Y., Dhenaut, L., De Schutter, E., Frugier, G. & Marty, A. Short-range and long-range chloride channel-mediated interactions between cerebellum stellate cells. **Proceedings of the National Academy of Sciences of the United States of America**, doi:10.1073/pnas.1508475112 (2015).
- Zeefuhati, S.J., Torben-Nielsen, B. & De Schutter, E. Cerebellar nuclear neurons use time and rate coding to transmit Purkinje neuron pauses. **PLoS Comput Biol 11**, e1004641, doi:10.1371/journal.pcbi.1004641 (2015) (IF=4.475).
- Wanner, A.A., Genoud, C., Masset, T., Porto, M.P., Murthy, V.N. & Friedrich, R.W. Surround inhibition and lateral excitation control spatial phase selectivity of cerebellar Purkinje cells in zebrafish. **Proceedings of the National Academy of Sciences of the United States of America**, doi:10.1073/pnas.1508232112 (2015).
- Wolfe, M.A., Biczulski, D., Torben-Nielsen, B. & Greenberg, M. D. A Screen Reformulation of the Green's function Formalism Allows Efficient Simulation of Morphological Neuron Models. **Neuroinformatics 13**, doi:10.1007/s12021-014-9252-4 (2015) (IF=3.01).
- Nagel, C., Gilsbertz, S., Dalwigk, C., Wang, L. Y., Akinrolabi, O., Tan, A., Ankerck, R., Spanka, R., Torben-Nielsen, B., White, A. F. & Leinenweber, A. Genetic and functional characterization of a conserved neuronal voltage-gated sodium channel. **Nature Neuroscience 18**, 1537-1545, doi:10.1038/nn.4130 (2015).

4.2 Books and other one-time publications

Nothing to report

4.3 Oral and Poster Presentations

Oral Presentations

- Kaneko, G., Yoshioka, M. & De Schutter, E. Implementation of Parallel Spatial Stochastic Reaction-Diffusion Simulation in STEPS. In CNS-2015 Meeting, Prague, Czech 2015).
- Kaneko, G., Yoshioka, M. & De Schutter, E. Accurate Approximation to Stochastic Reaction Diffusion on Unstructured Meshes in STEPS. In CNS-2015 Meeting, Prague, Czech 2015).
- Sudhakar, S. K., Torben-Nielsen, B. & De Schutter, E. The effect of synchronized pauses on the coding strategies of cerebellar nuclear neurons. In Society of Neuroscience 2015, Chicago, USA (2015).
- Sudhakar, S. K., Torben-Nielsen, B. & De Schutter, E. Cerebellar nuclear neurons use time and rate coding to transmit Purkinje neuron pauses. In Society of Neuroscience 2015, Chicago, USA (2015).
- Torben-Nielsen, B. & De Schutter, E. Dendrites: Bigger is faster. In Bernstein Conference on Neuroscience 2015 Meeting, Prague, Czech 2015).
- Torben-Nielsen, B. & De Schutter, E. Plug-and-play cell model groups for faster simulations. In Society of Neuroscience 2015, Chicago, USA (2015).
- Vitale, N., Torben-Nielsen, B., Negrello, M., De Schutter, E., Yarom, Y. & Lockwood, M. G. Dendritic arrangement rather than sizes determines the synaptic response of cerebellar cortical interneurons. In Society for Neuroscience 2015, Chicago, USA (2015).
- Zang, Y. & De Schutter, E. The cerebellar cortex as a Purkinje cell dynamic spike generator and computation: a model-equivalent. In CNS-2015 Meeting, Prague, Czech (2015).

5. Intellectual Property Rights and Other Specific Achievements

Nothing to report

6. Meetings and Events

6.1 Seminar Course

OIST Computational Neuroscience Course 2015

- Date: June 26 - 29, 2015
- Venue: Seaside House, OIST
- Organizers: Erik De Schutter, Kenji Doya & Minoru Matsuzaki
- Co-sponsored by the European Commission, Search Framework Programme via the European project CDINF-FP7-ICT-601167.
- Speakers:
  - Nelia Cohen (University of Leeds, UK)
  - Dora De Schutter (OIST)
  - Stefan Dodt (Dolomite)
  - Eugene Jedwabin (Bruker Corporation, USA)
  - Bernd Kuhn (OIST)
  - Ian Parnavelas (University Leeds, UK)
  - Tuba Nishimura-Nakamura (Japan Physiological Sciences, Japan)
  - Steve Prescott (University of Toronto, Canada)
  - Jonathan Rubin (University of Pittsburgh, USA)
  - Jackie Schiller (Technion, Israel)
  - Greg Stephens (OIST)
  - Tomoki Tokuno (Hamamatsu, Japan)
  - Tom Sejnowski (Salk Institute, USA)
  - Yoko Yazaki (Japan Science and Technology Agency, Japan)
  - Yoko Yazaki-Sugiyama (OIST, Japan)

6.2 Internal Seminar

Title: Understanding how the brain does motor control

- Date: 2015-07-07
- Venue: OIST Campus Lab1, C700
- Speaker: Dr. Sergio Verduzco, OIST Researcher

7. Other

Nothing to report.