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OIST Computational Neuroscience Course (OCNC 2025) | Monday, June 23, 2025 (All day) to Thursday, July 10, 2025 (All day)

Computational Neuroscience Unit (Erik De Schutter)

FY2018 Annual Report

Computational Neuroscience Unit
Professor Erik De Schutter

Front row, left to right: Chie Narai, Anzhelika Koldaeva (rotation student), Sarah Nagasawa, Dr. Andrew Gallimore, Dr. Peter Bratby, Mizuki Kato, Dr. Weiliang Chen, Dr. Sergio Verduzco
Back row, left to right: Sanghun Jee (intern), Maria Astrakhan (rotation student), Dr. Guido Klingbeil, Dr. Sungho Hong, Prof. Erik De Schutter, Dr. Yunliang Zang, Dr. Mykola Medvidov, Dr. Iain Hepburn
Missing: Dr. Alexey Martyushev and Dr. Criseida G. Zamora-Chimal

Abstract

We use computational, data-driven methods to study how neurons and microcircuits in the brain operate. We are interested in how fundamental properties, such as a neuron's morphology and its excitability, interact with one another during common neural functions like information processing or learning. Most of our models concern the cerebellum as this brain structure has a relatively simple anatomy and the physiology of its main neurons has been studied extensively, allowing for detailed modeling at many different levels of complexity.

1. Staff

- Molecular modeling
  - Iain Hepburn, Technical Staff
  - Andrew Gallimore, Researcher
  - Criseida Zamora, Researcher (till December 2018)
  - Sarah Yukie Nagasawa, PhD Student
- Cellular modeling
  - Sungho Hong, Group Leader
  - Yunliang Zang, Researcher
  - Alexey Martyushev, Researcher
- Network modeling
  - Sergio Verduzco, Researcher
  - Peter Bratby, Researcher
  - Mykola Medvidov, Staff Scientist
  - Mizuki Kato, PhD Student
- Software development
  - Weiliang Chen, Staff Scientist
  - Guido Klingbeil, Researcher
- Visiting Researcher
  - Jihwan Myung, Taipei Medical University
  - Samuel Melchior, EPFL
  - Tristan Carel, EPFL
- Visiting Research Student
  - Audrey Denizot (June-October 2018)
- Research Interns
  - Sanghun Jee (October 2018 - January 2019)
  - Pablo Santana Chacon (From January 2019)
  - Mari Shishikura (Februry-March 2019)
- Rotation Students
  - Maria Astrakhan, Student(Term 1)
  - Anzhelika Koldaeva, Student (Term 1)
  - Lorena Andreoli, Student (Term 2)
  - Xiaochen Fu, Student (Term 3)
- Research Unit Administrator
  - Chie Narai

2. Collaborations

- **Theme: Cerebellar physiology, multiple themes**
  - Type of collaboration: Scientific collaboration and graduate program
  - Researchers:
    - Professor M. Giugliano, University of Antwerp, Belgium
    - Professor D. Snyders, 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
    - A. Ignashchenkova, University of Tübingen, Germany
    - Dr. M. Junker, University of Tübingen, Germany
    - A. Schmigdin, University of Tübingen, Germany
- **Theme: Human Brain Project: simulator development**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Prof. F. Schürmann, École Polytechnique Fédérale de Lausanne, Switzerland
    - Dr. S. Melchior, École Polytechnique Fédérale de Lausanne, Switzerland
    - Dr. T. Carel, École Polytechnique Fédérale de Lausanne, Switzerland
- **Theme: Molecular identification of cerebellar signaling pathways and cerebellar optogenetics**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor K. Tanaka, Korea Institute for Science and Technology (KIST), Korea
- **Theme: Quantitative molecular identification of hippocampal synapses**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Prof. Dr. Silvio O. Rizzoli, Medical University Göttingen, Germany
- **Theme: Cerebellar molecular layer interneurons**
  - Type of collaboration: Joint research
  - Researchers:
    - Professor Alain Marty, Université Paris 5 René Descartes, France
- **Theme: Cerebellar anatomy and physiology**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor C. De Zeeuw, Erasmus Medical Center, Rotterdam, The Netherlands
    - Professor L.W.J. Bosman, Erasmus Medical Center, Rotterdam, The Netherlands
    - Dr. 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. Dieudonné, Ecole Normale Supérieure, Paris, France
- **Theme: Circadadian rhythm generation**
  - Type of collaboration: Scientific collaboration
  - Researchers:
    - Professor J. Myung, Taipei Medical University, Taiwan

3. Activities and Findings

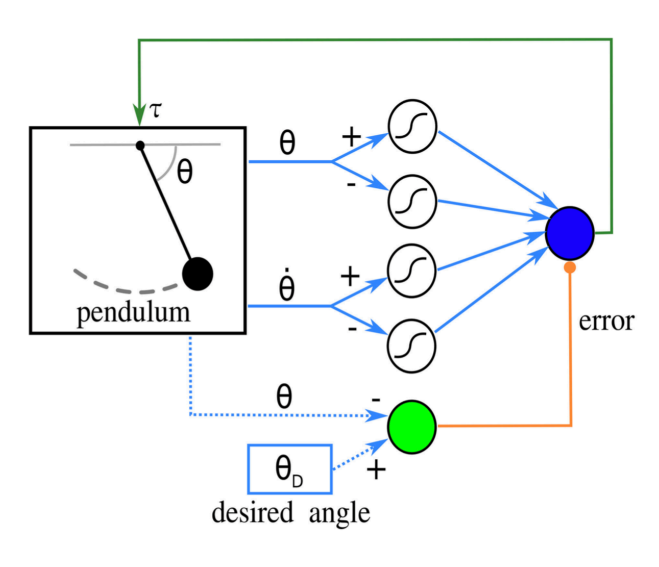
3.1 Software Development

Draculab: simulator for firing rate neural networks with delayed connections

Draculab was born from a project whose requirements were not met by any other simulator. Those requirements were:

- Firing rate units that operate as continuous-time dynamical systems, connected with transmission delays.
- Experimental types of units and synapses, with frequent modifications happening.
- Simulations where neural controllers interact with a physical system, implementing closed-loop
- control.

Draculab is written entirely in Python, with certain key functions coded in Cython (Verduzco Flores and De Schutter, 2019). Development environments such as Spyder (https://www.spyder-ide.org/), or the Jupyter Notebook (https://jupyter.org/), are well suited for working with Draculab. The interface uses standard functions that create units, connect them, and run simulations. These functions are configured using parameter dictionaries as their arguments. Users can launch their first simulations within minutes (see section 2).



A simple example requiring about 50 lines of Draculab code is shown in Figures 1-2. The pendulum sends angle and angular velocity signals to four sigmoidal afferent units, which in turn send inputs to a control unit (blue circle). The control unit produces a torque on the pendulum based on this input. The source unit, in green, calculates an error signal from the desired and the current angle. The derivative of this error is used by the learning rule.

Figure 1: Diagram of a simple network for closed-loop simulation (from Verduzco Flores and De Schutter, 2019).

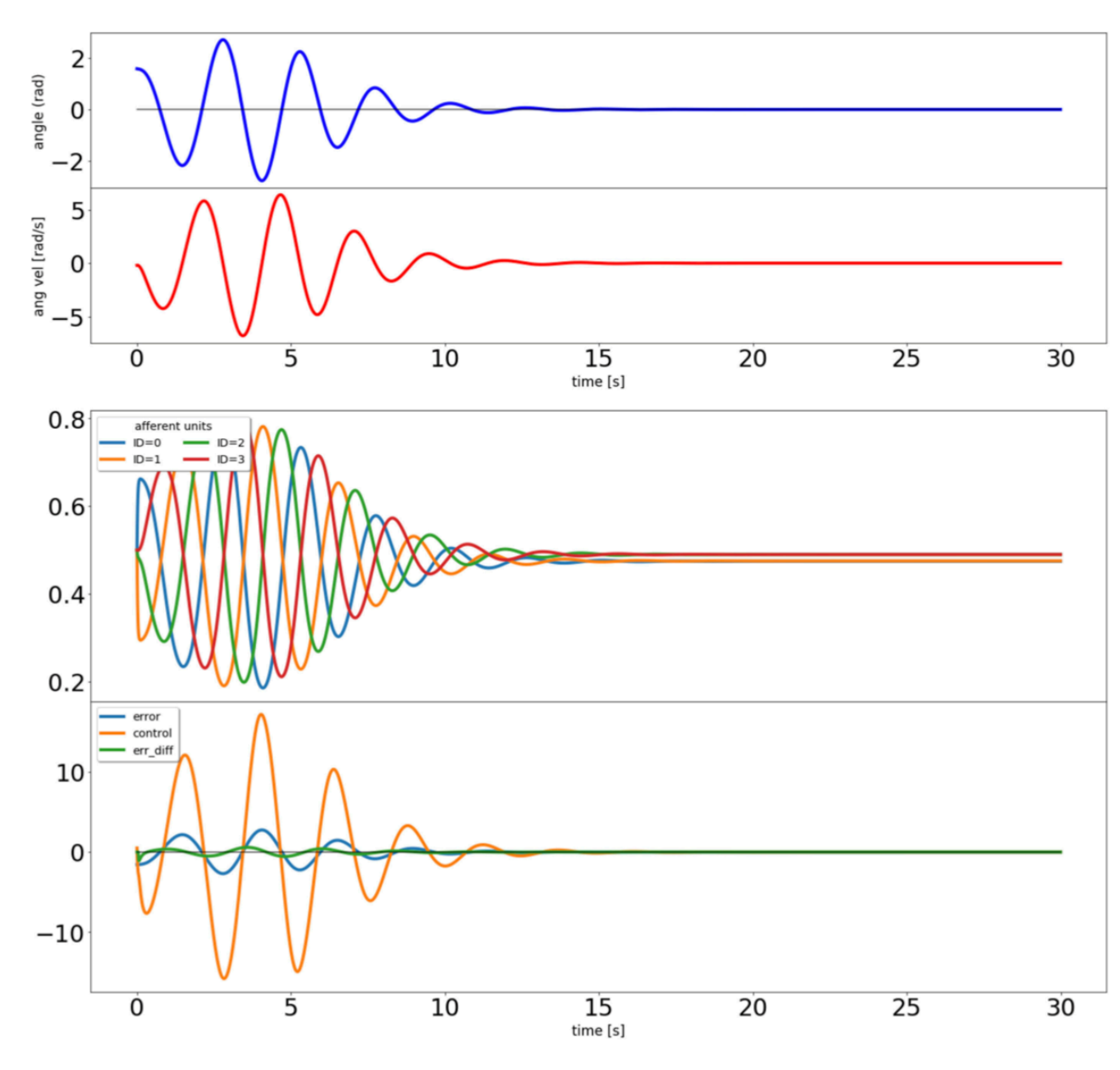


Figure 2: Output of the closed loop simulation using an input correlation rule to adjust the synaptic weights of the afferent inputs to the control unit (from Verduzco Flores and De Schutter, 2019).

3.2 Molecular mechanisms of synaptic plasticity

Frequency dependence of induction in a model of long-term depression

Cerebellar long-term depression (LTD) is a form of synaptic plasticity dependent on postsynaptic Ca^{2+} changes. A fundamental question is how LTD is selectively induced by specific numbers of Ca^{2+} pulses and which are the frequency and duration of this train of pulses required for LTD induction. The molecular mechanism which leads the integration of postsynaptic Ca^{2+} pulses in the LTD signaling network has not been elucidated either. Unfortunately, these matters have not been studied systematically at the experimental level. Recent publications have shown that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is required for LTD induction. Additionally, protein kinase C (PKC), CaMKII, and MAPK play an important role to transduce the frequency of Ca^{2+} pulses into their enzymatic activity levels; however, it is still unknown which enzymes are involved in decoding Ca^{2+} pulses in LTD.

We have extended a stochastic model of LTD by adding the molecular network regulating CaMKII activity and its activation (Zamora Chimal and De Schutter, 2018) (Figure 3).

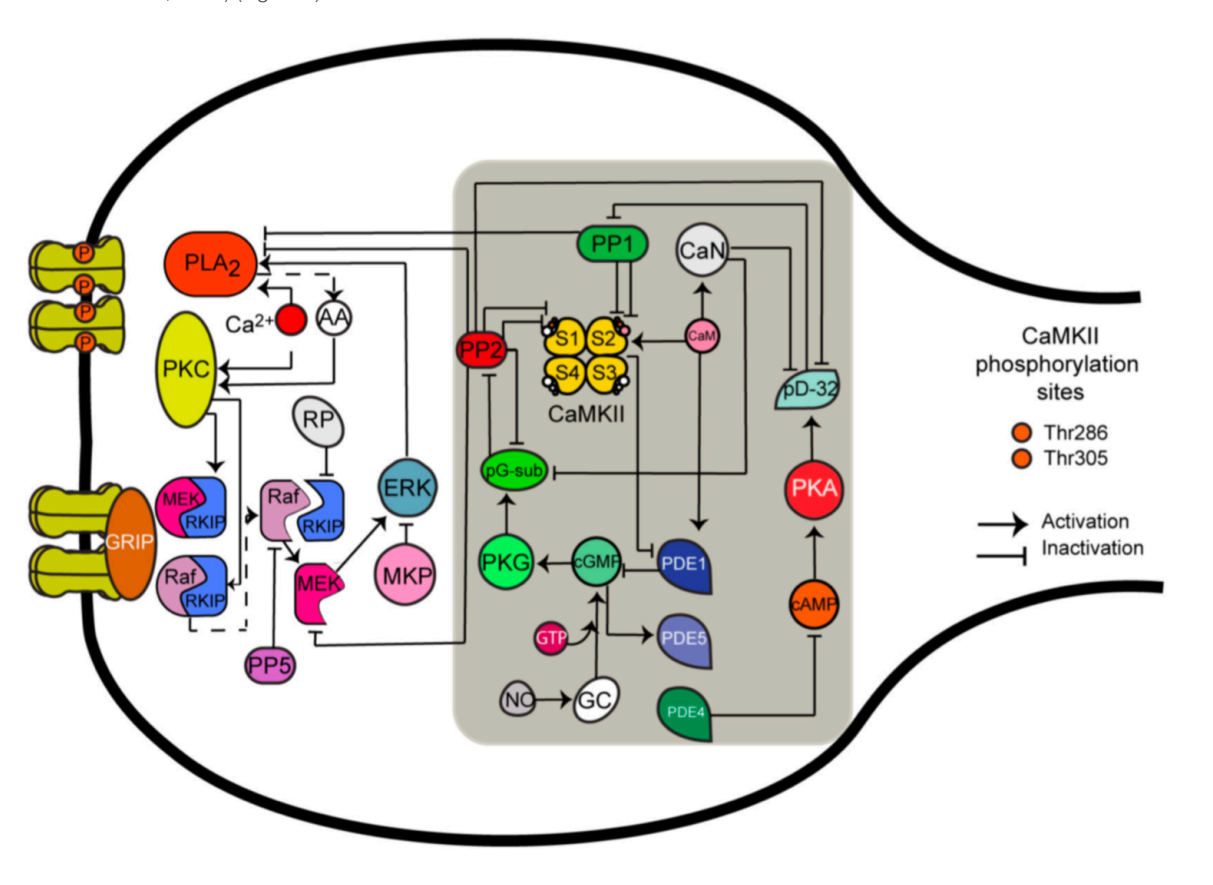


Figure 3: The long-term depression signaling pathway simulated by Zamora Chimal and De Schutter (2018), including the molecular network regulating CaMKII activity at postsynaptic density. Parts of this model were developed by us previously (Hepburn et al., *Frontiers in Molecular Neuroscience* 2017), the parts in the grey box were added in this study.

We solved this model with the STEPS simulator (Hepburn et al., *BMC Systems Biology* 2012) to include the effect of biochemical noise in LTD. This stochastic model is bistable: it predicts that at single spines either full LTD or no LTD is produced and the graded LTD observed in vivo is the result of averaging over many synapses (Hepburn et al., *Frontiers in Molecular Neuroscience* 2017).

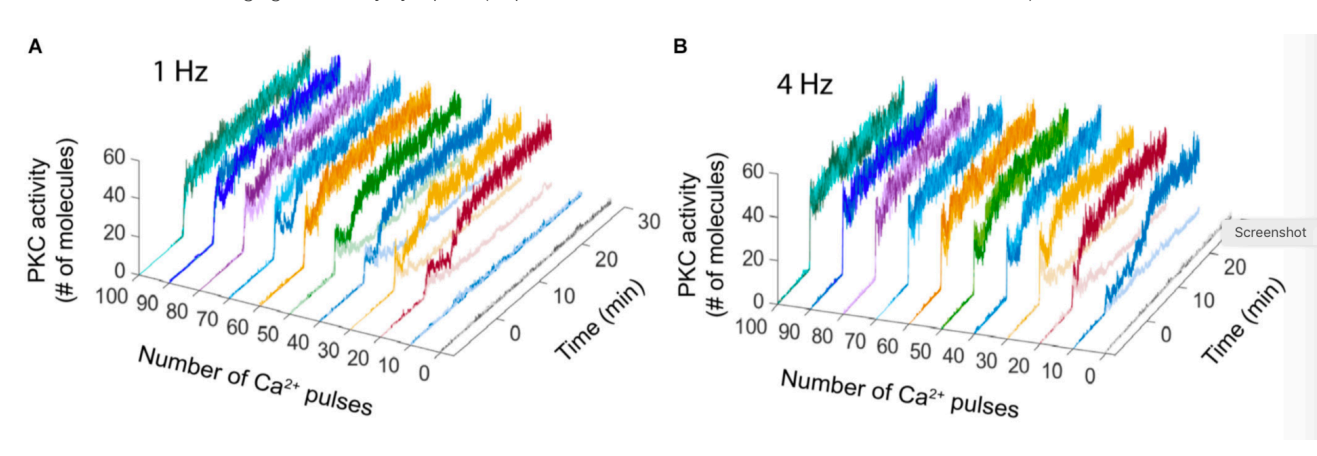


Figure 4: PKC activity over time shows bistability. Raw data of PKC over time in the LTD signaling network at different number of Ca^{2+} pulses. Two different trials were chosen randomly for every number of Ca^{2+} input. (**A**) Bistability of PKC activity is clearly visible from 20 to 50 calcium pulses at 1 Hz and (**B**) from 10 to 30 pulses at 4 Hz (from Zamora Chimal and De Schutter, 2018).

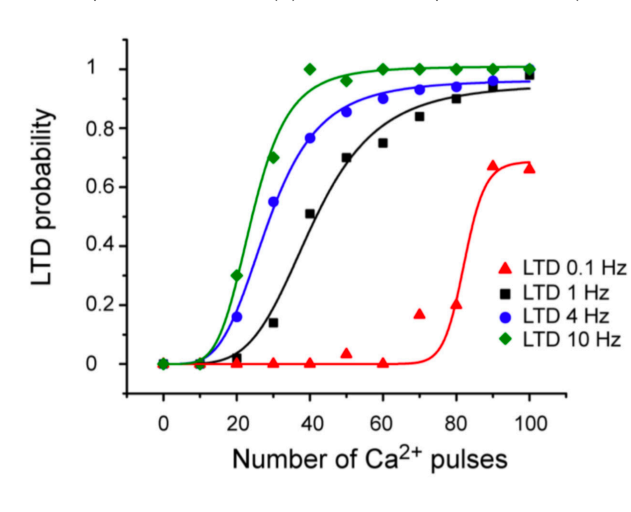


Figure 5: LTD probability over number of Ca^{2+} pulses for different simulation frequencies (from Zamora Chimal and De Schutter, 2018).

We found that the number of Ca^{2+} pulses used to induce LTD affected this bistability: there was a specific ranges of Ca^{2+} pulses for which the response was bistable, below this range there was never LTD and above it there was always LTD (Figure 4).

Moreover, this bistable range depended on the stimulation frequency (Figures 4-5) and on amplitude and width of the Ca^{2+} pulses (not shown). In addition to PKC, ERK and CAMKII enzyme activity also strongly depended on the number of Ca^{2+} pulses (not shown).

Finally we investigated the role of different phosphorylation sites in CAMKII (Figure 6) on LTD induction. We predict that LTD is only weakly induced when its Thr286 phosphorylation site has been deleted, but deletion of the Thr305 autophosphorylation site has little effect (Figure 7)

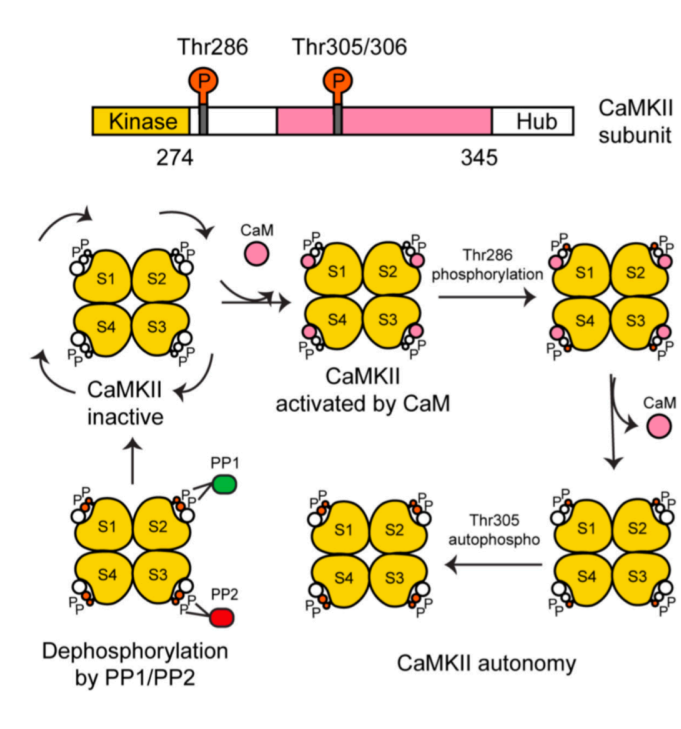


Figure 6: Different phosphorylation sites in CAMKII (top) and all possible states of CaMKII activation in the model (bottom). (from Zamora Chimal and De Schutter, 2018).

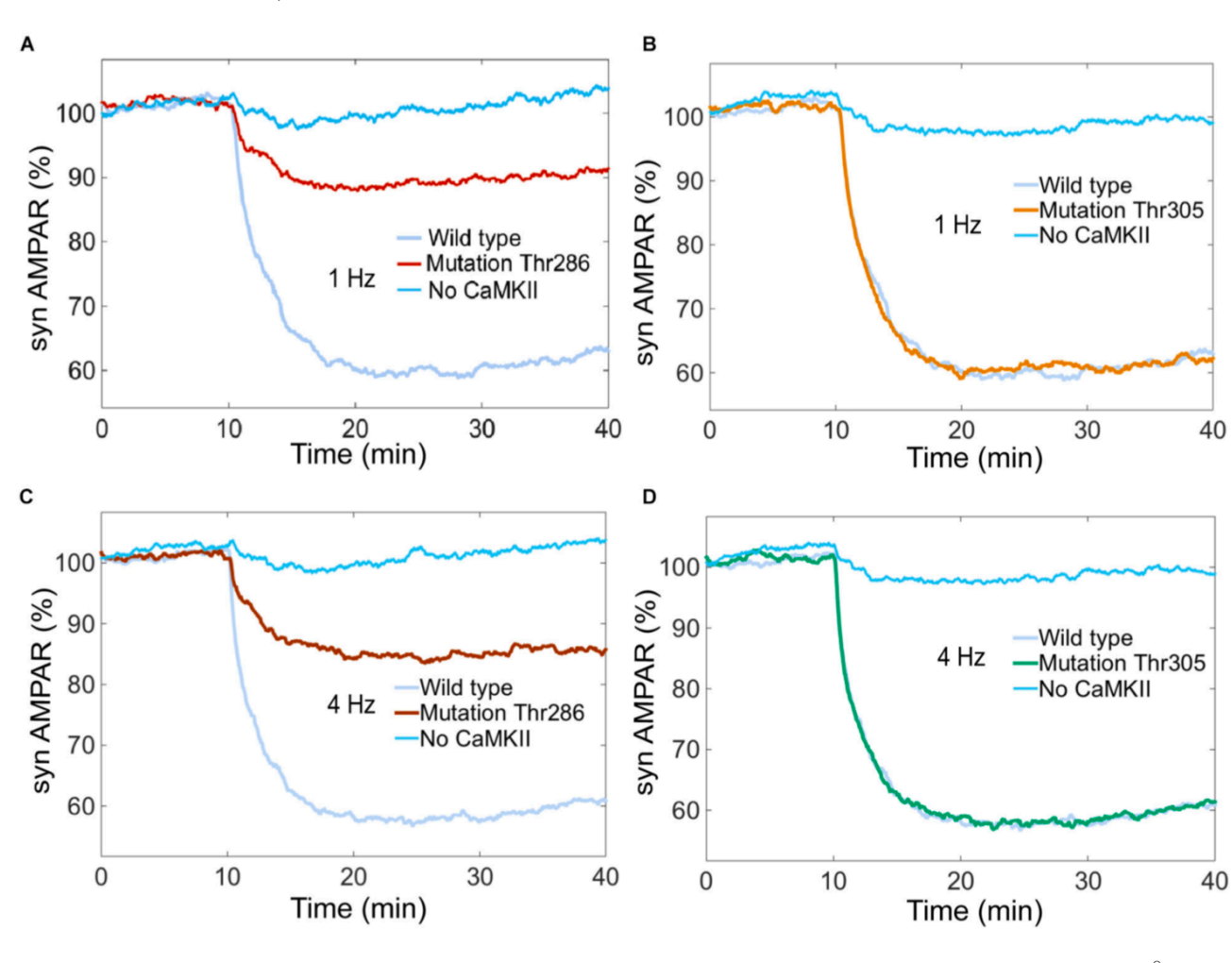


Figure 7: Thr286 phosphorylation site has an important effect on LTD induction. Time courses of depression induced by 100 of Ca^{2+} pulses at 1 and 4 Hz. Each curve shows the mean time course calculated for 100 iterations of the model. The magnitude of the depression was measured as percentage for synaptic AMPARs when the system is complete (wild type) and mutated at the Thr286 or Thr305 sites. (**A**) and (**C**) show LTD impairment when Thr286 phosphorylation site has been deleted for calcium stimulation at 1 and 4 Hz, respectively. (**B**) and (**D**) do not show any change in the amount of LTD when Thr305 phosphorylation site has been deleted. (**A–D**) show that CaMKII activity is required for LTD induction. (from Zamora Chimal and De Schutter, 2018).

3.3 Cellular mechanisms regulating firing and synaptic properties of neurons

Voltage- and branch-specific climbing fiber responses in a Purkinje cell model

Climbing fibers provide instructive signals driving cerebellar learning, but mechanisms causing the variable climbing fiber responses in Purkinje cells are not fully understood. We built a new experimentally validated Purkinje cell model (Zang et al., 2018) (Figure 8).

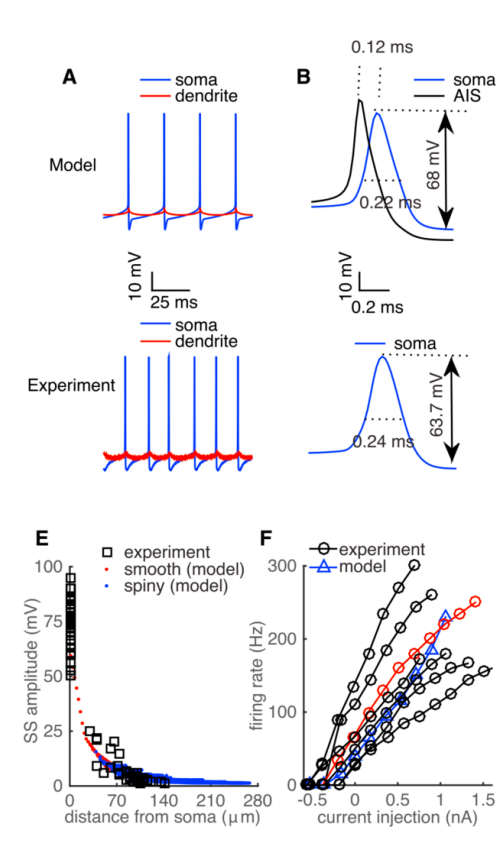


Figure 8: Model properties compare well with experimental data.(**A**) Spontaneously firing simple spikes and dendritic membrane potentials (103 μm from soma) from the model and experiments (dendritic site is ~100 μm from soma). (**B**) A single simple spike from the model and experiments. The spike at the axon initial segment (AIS) is aligned to measure the axosomatic delay in the model. (**E**) Distance-dependent decay of simple spike amplitudes in the model and experimental data (Ohtsuki et al., *Neuron* 2012). (F) The F-I curve of the model compared with experimental data. (from Zang et al., 2018).

When Purkinje cells receive synaptic inputs from climbing fibers, stereotypical complex spikes occur at their somas. Climbing fiber responses at different sites of a spontaneously firing Purkinje cell model are shown in Figure 9A. The peak dv/dt of the first spikelet in the complex spike is ~270 mV/ms larger than that of the simple spike, as confirmed by in vitro experimental data (Figure 9B).

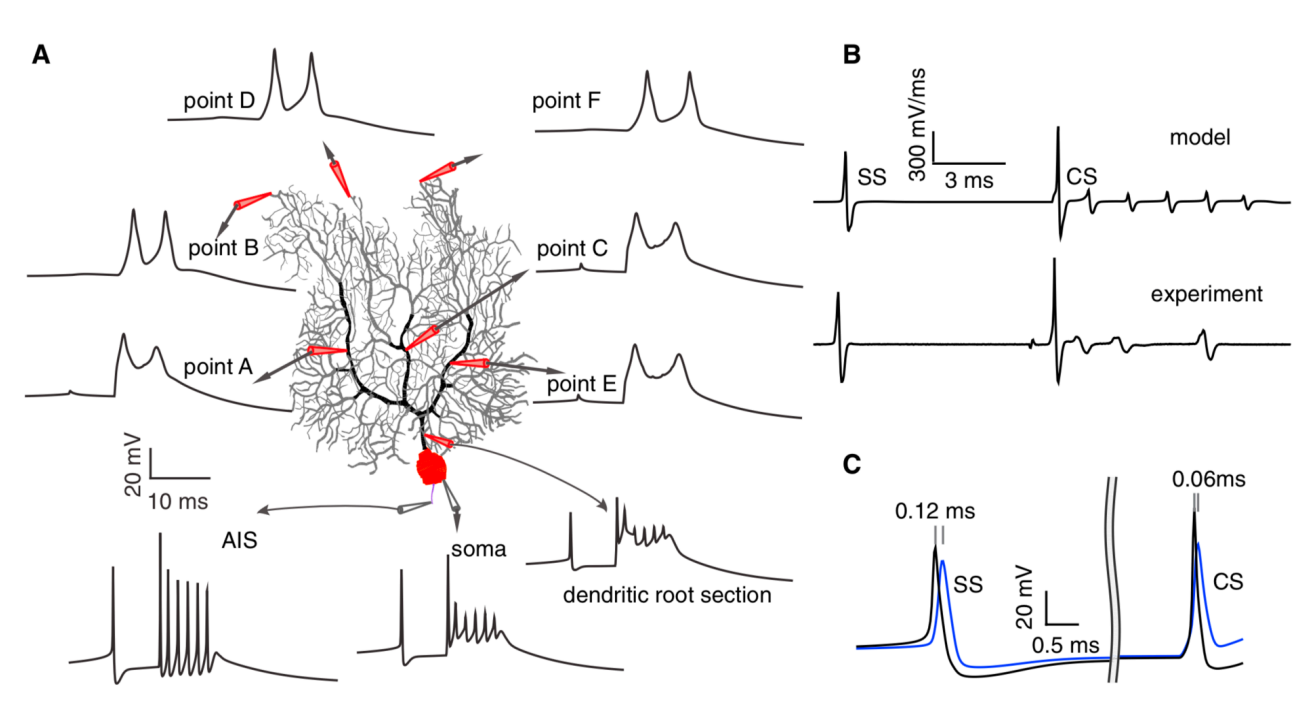


Figure 9: Generation of climbing fiber responses in the Purkinje cell model. (**A**) Climbing fiber responses at different sites in the Purkinje cell model. Two sites on each main branch are selected. (**B**) The peak dv/dt of the first complex spike spikelet increases compared with a simple spike in both model and experiment (Warnaar et al., *Front. Cell. Neurosci.* 2015).(**C**) The axosomatic delay of the first spikelet in the complex spike decreases compared with a simple spike (from Zang et al., 2018).

We systematically explored how different voltage states, caused by varying the somatic holding current, regulate climbing fiber-evoked dendritic responses and analyzed the biophysical mechanisms. Depolarization facilitates higher peaks of dendritic responses with further propagation into distal spiny dendrites (Figure 10). In distal spiny dendrites, axial currents from proximal smooth dendrites are the only current sources that can depolarize to approach the Ca^{2+} spike threshold and trigger a dendritic spike. When the soma is held at ⊠76 mV (Figure 10 left panels), the A-type Kv4 current is larger than the P-type Ca^{2+} current in spiny dendrites . Consequently, axial currents cause only small passive depolarizations in spiny dendrites. In smooth dendrites, the climbing fiber provides powerful synaptic input to depolarize passively the dendrite. Voltage responses decrease with distance from the soma in the whole dendrite. As the soma is held at ⊠70 mV (Figure 10 central panels), dendritic spikes occur in part of the dendritic tree (the left half, proximal to the soma), where the voltage responses now increase with distance from the soma. With depolarization of the soma to ⊠60& mV (Figure 10 right panels), the Kv4 current gradually inactivates and becomes smaller than the P-type Ca^{2+} current in both smooth and spiny dendrites during the initial depolarization phase. As a result, the P-type Ca^{2+} current depolarizes the dendrites and activates more Ca^{2+} channels in a positive-feedback loop until the Kv3 current is highly activated to repolarize the spikes. Dendritic spikes occur globally and their peaks increase with distance from the soma. These processes makes the energy consumed during a complex spike (CS) also voltage dependent.

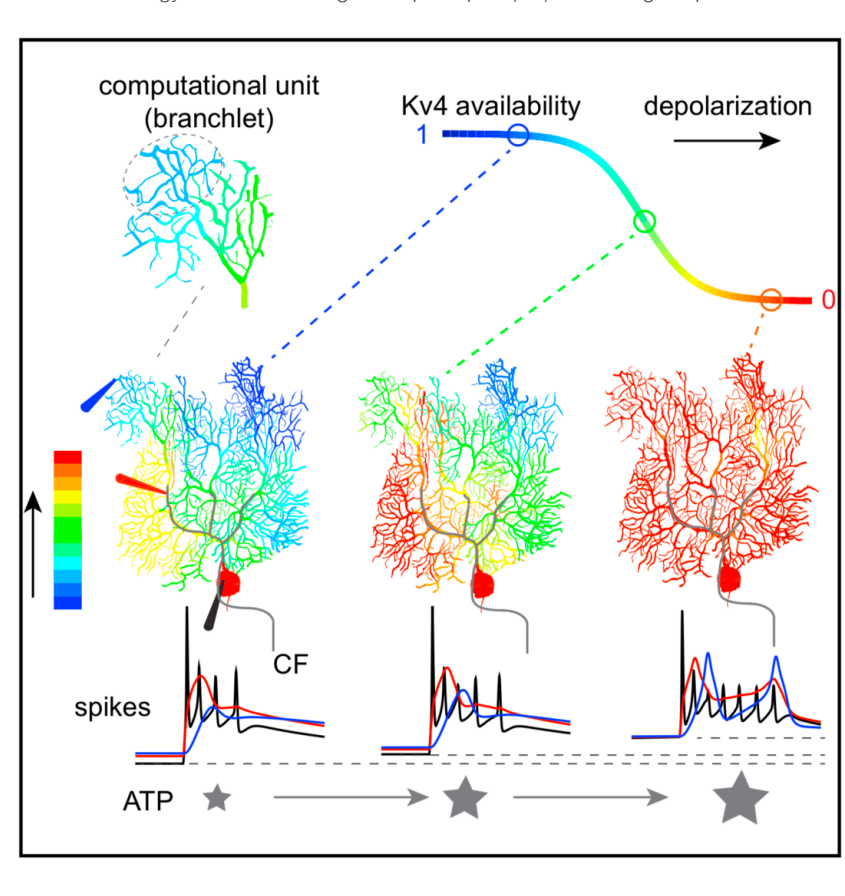


Figure 10: Voltage states regulate climbing fiber-evoked dendritic spike generation and propagation and complex spike energy use (bottom). From left to right column, the holding potentials are -76, -70 and -60 mV respectively. Middle panels show voltage maps in dendrite and soma while bottom panels show voltage recordings at indicated sites in soma and dendrite (graphical abstract from Zang et al., 2018).

Purkinje cell dendrites exhibit inhomogeneous excitability with individual branches as computational units for climbing fiber input. The variability of somatic complex spikes and their duration can be explained by voltage state, climbing fiber activation phase, and instantaneous climbing fiber firing rate (not shown). Concurrent clustered synaptic inputs affect complex spikes by modulating dendritic responses in a spatially precise way leading to paradoxical effects: 5 parallel fiber synapses activated together with the climbing fiber lead in Figure 11 to a longer somatic complex spike than 20 parallel fiber synapses activated similarly.

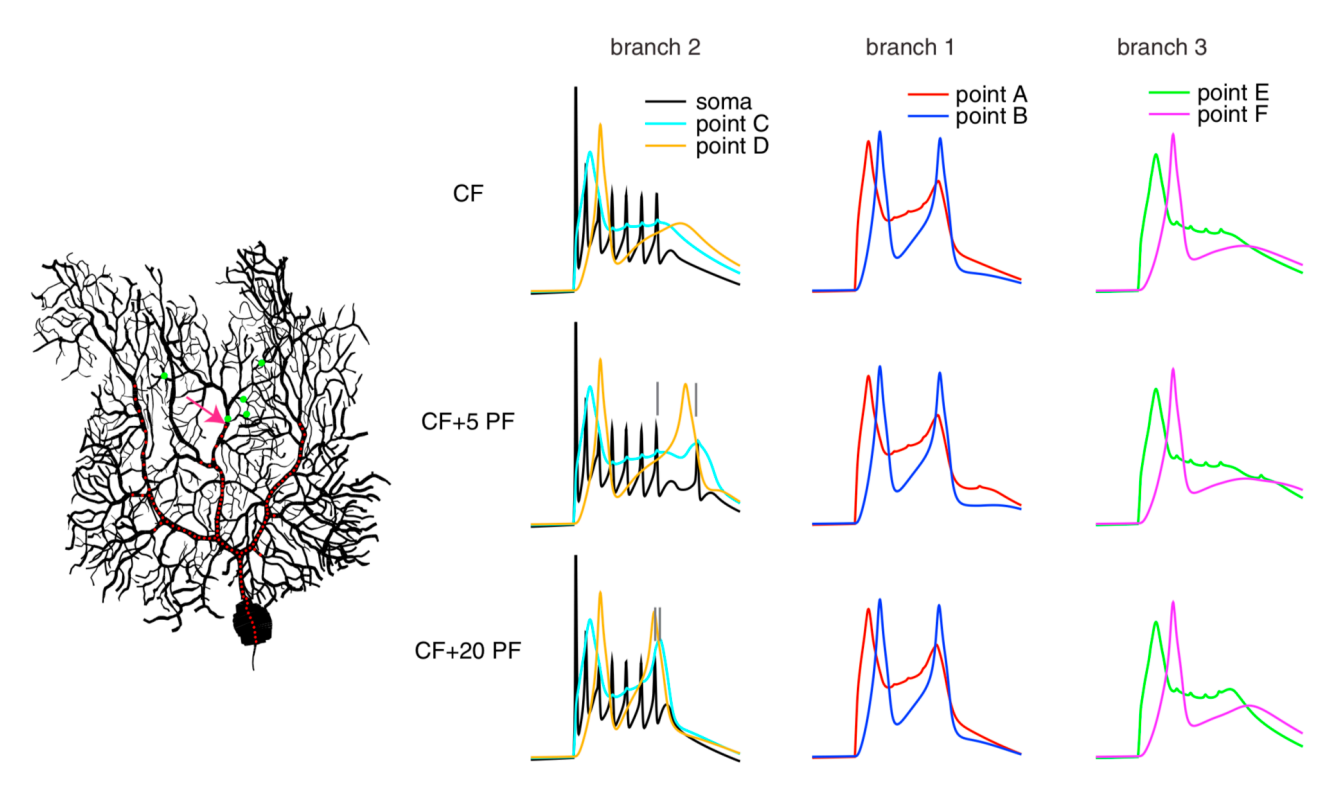


Figure 11: Simultaneous clustered parallel fiber synaptic input regulates the climbing fiber-evoked somatic complex spike by locally modulating the dendritic responses. Somatic and dendritic responses with only climbing fiber input (red dots), climbing fiber input + 5 parallel fiber synaptic inputs, and climbing fiber input + 20 parallel fiber synaptic inputs are shown from top to bottom. Parallel fiber synapses are randomly distributed on the indicated dendritic child branchlet (green dots). (from Zang et al., 2018).

The voltage- and branch-specific climbing fiber responses can increase dendritic computational capacity and enable Purkinje cells to actively integrate climbing fiber signals. They also make it impossible to use the complex spike duration to detect the difference between complex spikes caused by single climbing fiber spikes from this caused by climbing fiber bursts (Mathy et al. *Neuron* 2009) as done by Yang and Lisberger (*Nature* 2014), because unobserved voltage changes will have similar effects.

4. Publications

4.1 Journals

1. C.G. Zamora Chimal and E. De Schutter: Ca^{2+} requirements for Long-Term Depression are frequency sensitive in Purkinje Cells. *Frontiers in Molecular Neuroscience* 11: 438 (2018).
2. Y. Zang, S. Dieudonné and E. De Schutter: Voltage- and Branch-specific Climbing Fiber Responses in Purkinje Cells. *Cell Reports* 24: 1536–1549 (2018).
3. N. Vrieler, S. Loyola, Y. Yarden-Rabinowitz, J. Hoogendorp, N. Medvedev, T.M. Hoogland, C.I. De Zeeuw, E. De Schutter, Y. Yarom, M. Negrello, B. Torben-Nielsen, and M.Y. Uusisaari: Variability and directionality of inferior olive neuron dendrites revealed by detailed 3D characterization of an extensive morphological library. *Brain Structure and Function* 224: 1677–1695 (2019).
4. S.O. Verduzco Flores and E. De Schutter: Draculab: A Python simulator for firing rate neural networks with delayed adaptive connections. *Frontiers in Neuroinformatics* 13:18 (2019).

4.2 Books and other one-time publications

Nothing to report

4.3 Oral and Poster Presentations

Oral Presentations

1. E. De Schutter, *Modeling the cell biology of learning*, OIST-KAIST Joint Symposium "Intelligence in Biological Systems and Its Application to Machines", Daejeon, Korea, June 4, 2018.

Poster Presentations

1. Y. Zang, *Using a detailed model to explore the importance of Purkinje cell dendrites for somatic firing properties*, International Symposium of the Society for Research on the Cerebellum and Ataxias, Taipei, Taiwan, May 2018.
2. C.G. Zamora Chimal, *A model of Long-Term Depression molecular network sensitivity to the frequency of Ca2+stimulus*, The International Conference on Systems Biology of Human Disease (SBHD), Los Angeles, USA, June 2018.
3. S. Hong, *Plasticity of information coding by cerebellar Purkinje cells during sensorimotor learning*, 27th Annual Computational Neuroscience Meeting, Seattle, USA, July 2018.
4. A.R. Gallimore, I. Hepburn, S.Y. Nagasawa, and E. De Schutter, *Realistic spatial modeling of vesicle trafficking in neurons*, Neuroscience 2018, San Diego, USA, November 2018.
5. Y. Zang,and E. De Schutter, *The interaction of Purkinje cell firing rate-dependent phase response curves and cerebellar network oscillations*, Neuroscience 2018, San Diego, USA, Nobember 2018.

5. Intellectual Property Rights and Other Specific Achievements

Nothing to report

6. Meetings and Events

6.1 OIST Computational Neuroscience Course 2018

- Date: June 25- July 12, 2018
- Venue: OIST Seaside House
- Organizers: Erik De Schutter (OIST), Kenji Doya (OIST), Bernd Kuhn (OIST), and Jeff Wickens (OIST)
- Speakers:
  - Maxim Bazhenov (University of California San Diego, USA)
  - Michael Brecht (Bernstein Center for Computational Neuroscience Berlin, Germany)
  - Erik De Schutter (OIST)
  - Kenji Doya (OIST)
  - Shaul Druckmann (Stanford University, USA)
  - Karl Friston (Wellcome Trust Centre for Neuroimaging, UCL, UK)
  - Michele Giugliano (University of Antwerp, Belgium)
  - Robert Gütig (Max Planck Göttingen, Germany)
  - Mitsuo Kawato (ATR, Japan)
  - Bernd Kuhn (OIST)
  - Kazuhisa Shibata (Nagoya University, Japan)
  - Olaf Sporns (Indiana University, USA)
  - Greg Stephens (OIST)
  - Krasimira Tsaneva-Atanasova (University of Exeter, UK)
  - Yoko Yazaki-Sugiyama (OIST)

6.2 Computational Neuroscience Unit Seminar

- *Counting vesicular release events in simple synapse recordings*, Dr. Marty Alain, CNRS and Paris Descartes University, on 7th December 2018.
- *Applications of 3D electron microscopy in synapse remodeling research*, Dr. Kea Joo Lee, Korea Brain Research Institute, on 21st January 2019.
- *Connectomic reconstruction of mouse cerebellar molecular layer from serial electron microscope images*, Dr. Jinseop Kim, Korea Brain Research Institute, on 21st January 2019.

7. Other

Nothing to report.