Slow pacemaking dynamics from fast activating kinetics in midbrain dopamine neurons

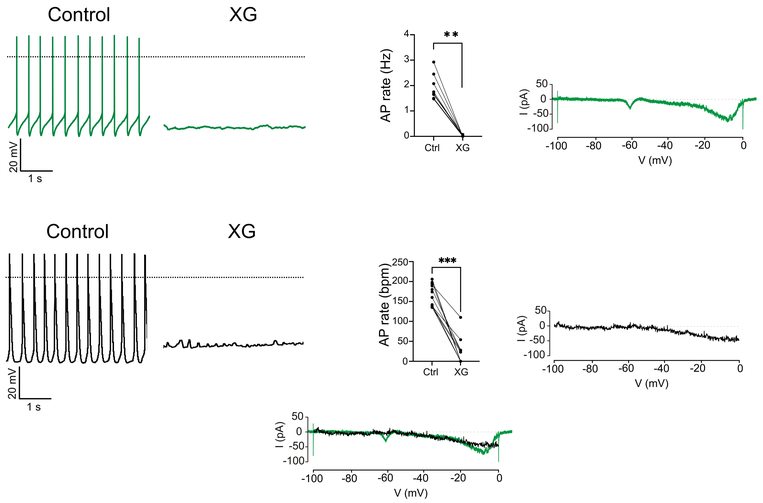
Arthur Fyon Oleksandra Pavlova Sofian Ringlet Alessio Franci Pietro Mesirca Matteo Mangoni
Nick Schaar Jochen Roeper Vincent Seutin* Guillaume Drion* **Kevin Jehasse***

Institute of Electrical Engineering and Computer Science, University of Liège, Belgium
GIGA-Neurosciences, University of Liège, Belgium
Institute of Neurophysiology, Neurosciences Center, Goethe University of Frankfurt am Main, Germany
Institut de Génomique Fonctionnelle, Université de Montpellier, France

Background and motivations

Pacemaker cells generate spontaneous rhythmic activity essential for life:

- Slow pacemakers (1–5 Hz) is observed in some neurons and cardiac cells, but **their underlying mechanism remains debated**.
- Sustaining such rhythmic firing requires **a small depolarizing current** active between spikes.
- **An XG-sensitive current with pacemaker-like properties** was recently identified in rodent midbrain dopaminergic neurons **(mDANs)** and in sinoatrial node **(SAN)** cells.
- This **shared mechanism** could bridge neurophysiology and cardiac physiology and reveal new targets for rhythm disorder therapies.



Top traces adapted from *Jehasse et al. 2021*.

In this poster: we model the XG-sensitive pacemaking current (I_{pace}) in a conductance-based model of mDANs and show that it **robustly sustains slow rhythmic activity**.

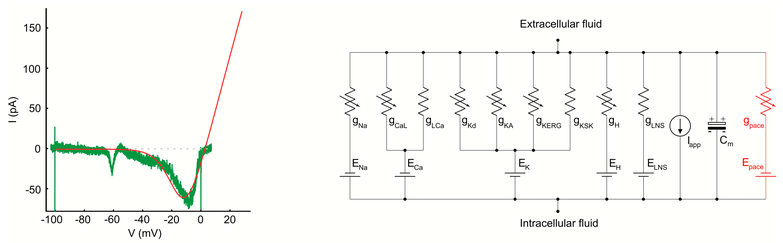
Modeling this pacemaking current

I_{pace} is modeled as an activation-only channel following the Hodgkin–Huxley formalism:

$$I_{pace} = \bar{g}_{pace} \cdot m_{pace} \cdot (V - E_{pace})$$

$$\dot{m}_{pace} = \underbrace{m_{pace,\infty}(V)}_{\text{Activation sigmoid}} - m_{pace} \qquad \underbrace{\tau_{m,pace}(V)}_{\text{Fit not feasible}}$$

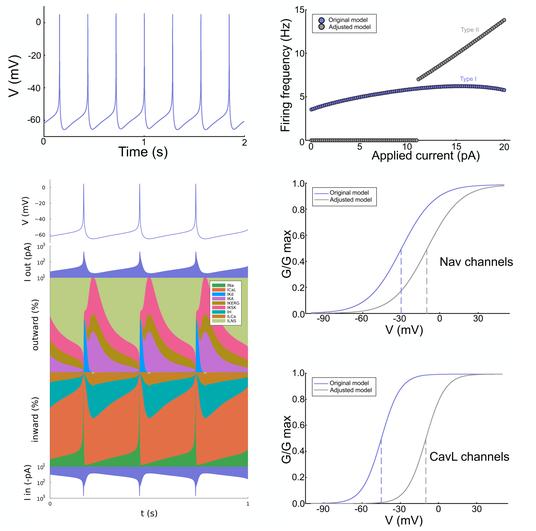
→ incorporated in the mDAN conductance-based model of *Yu and Canavier 2015*.



Current models fail to capture the mechanism of slow pacemaking

Slow pacemaking mechanism is difficult to infer in current models:

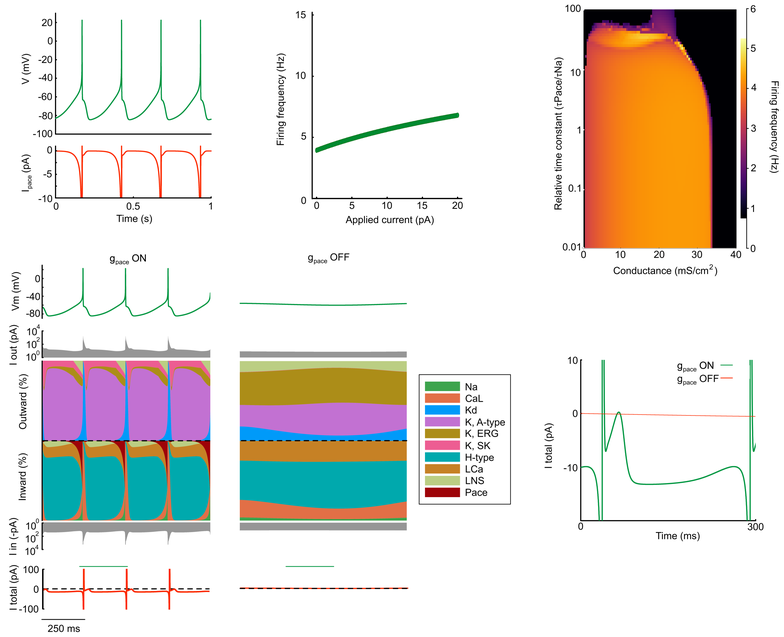
- Interspike depolarizing current is supported by Na and CaL currents:
  → inconsistent with experimental data [*Jehasse et al. 2021*].
- Half activations of these channels are too hyperpolarized vs. experimental data [*Seutin and Engel 2010*; *Durante et al. 2004*]:
  → readjusting them to physiological values breaks the pacemaking property.
- In physiologically constrained model, we need I_{pace}.



→ Therefore, we introduced I_{pace} into the **physiologically constrained model**.

Incorporating I_{pace} restores robust slow pacemaking

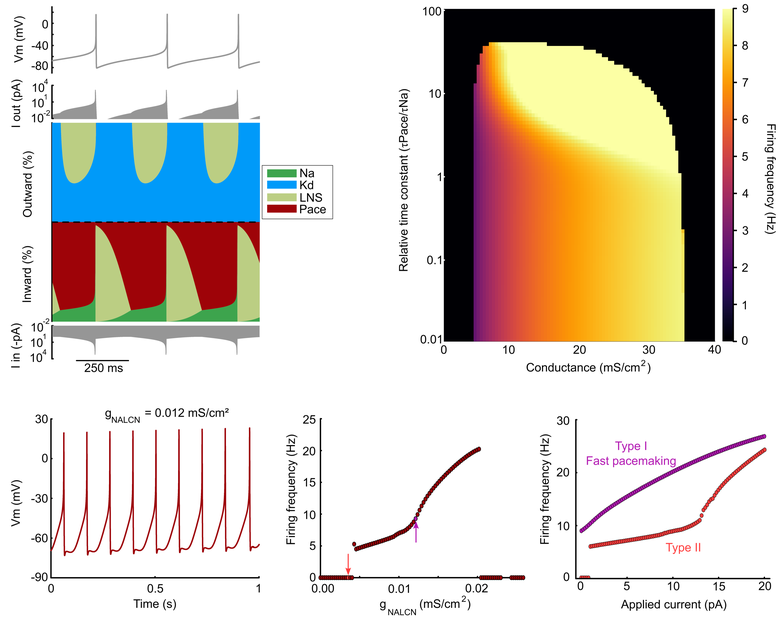
Incorporating I_{pace} restores slow pacemaking **for a wide range of conductance**.



→ as $\tau_{m,pace}$ **could not be fitted**, the model indicates that it must **fast**.

Minimal requirements to produce slow pacemaking

As I_{pace} robustly restores regular slow pacemaking, it raises the question of which ion channels are **essential to slow pacemaking**.



→ Only I_{Na}, I_{Kd} **and** I_{pace} are required to generate slow pacemaking.
→ **Same kinetics hypotheses** are observed in this minimal combination.
→ **A voltage-independent current** such as NALCN **cannot produce robust pacemaking**.

Conclusions and perspectives

- Current models **are unable** to explain the mechanism of **slow pacemaking** and rely on **nonphysiological parameters**.
- Incorporating I_{pace} supports **the hypothesis that this current might be a shared mechanism of slow pacemaking**.

Future work

- Verifying the hypothesis of a fast kinetic channel using dynamic clamp on mDANs.
- Identifying the molecular identity of channels supporting I_{pace}.
- Validating this mechanism in SAN cell models.

References

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*: Equal contribution Kevin.Jehasse@uliege.be afyon@uliege.be