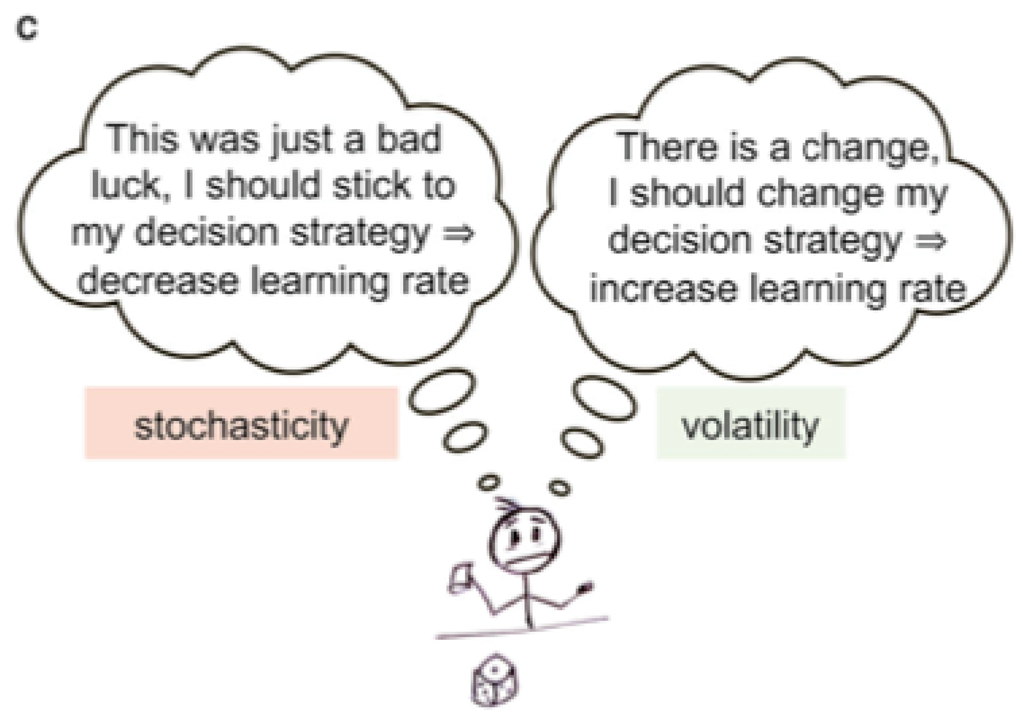
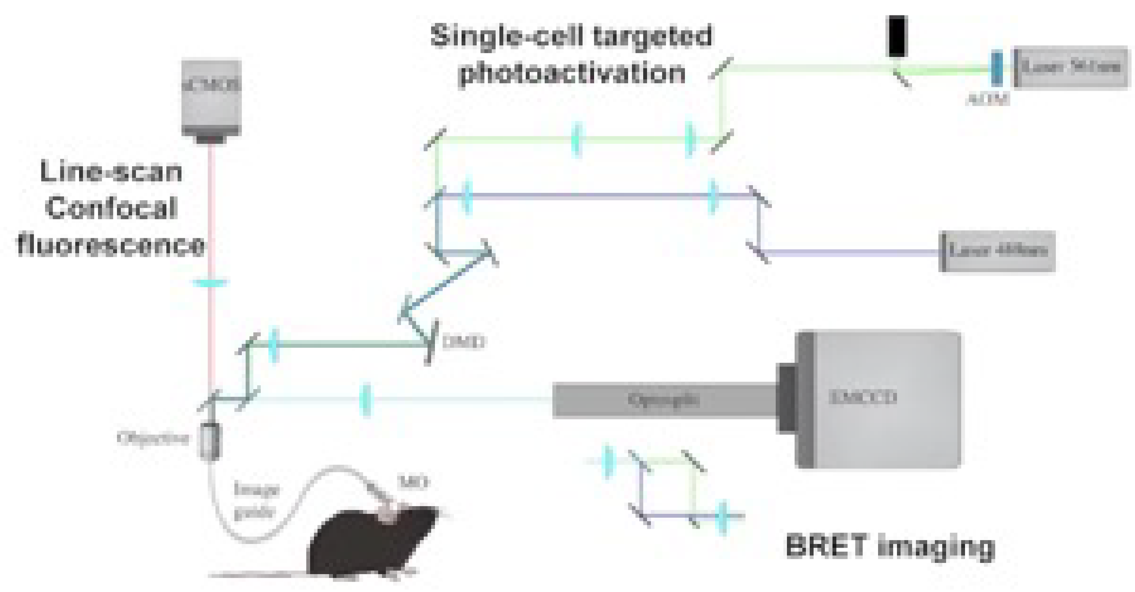
The chemistry of choice: linking intracellular plasticity to learning under uncertainty

Jérémie Naudé,
Physiopathologie de la transmission synaptique
Institut de Génomique Fonctionnelle, Montpellier

Animals adapt their learning rate to the statistics of their environment [1]: learning fast when contingencies change (volatility) while filtering noisy fluctuations (stochasticity). How this adaptation emerges from the biochemistry of the synapse remains unknown. Behavioral models (reinforcement-learning) reproduce this flexibility with abstract algorithms, while detailed biophysical models capture the molecular machinery without linking it to adaptive learning [2].

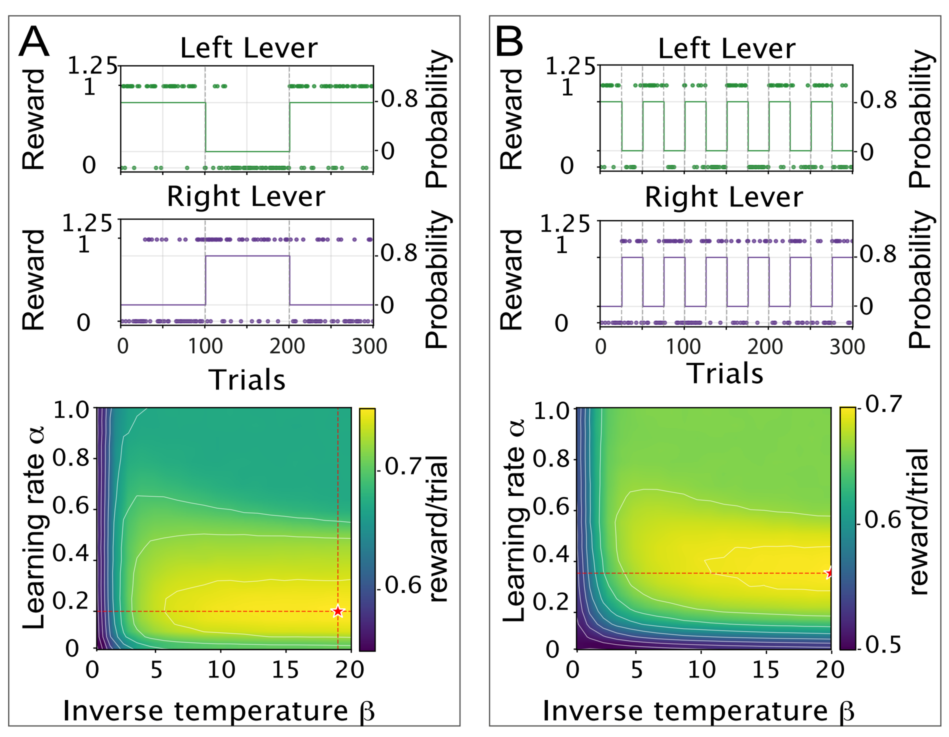


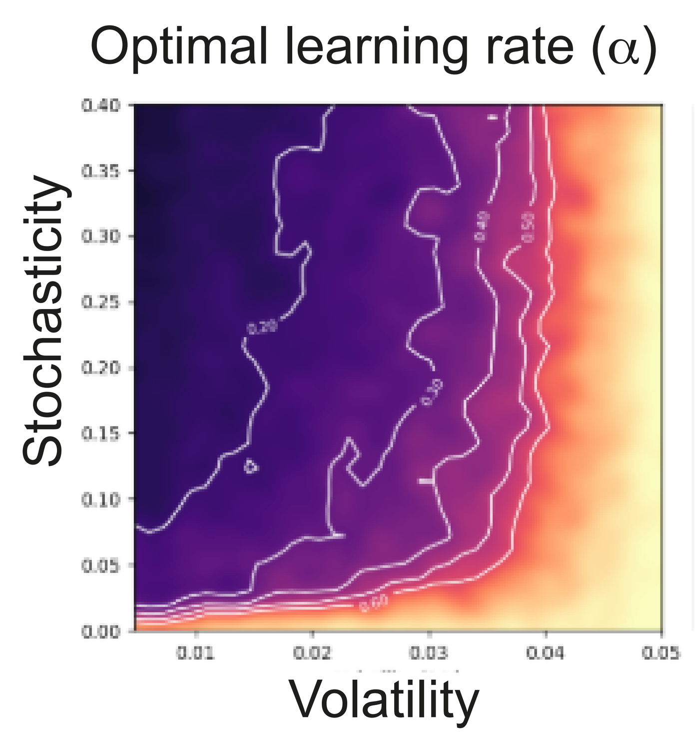


I Cognitive models

Preliminary analysis of reinforcement learning models
$V(t+1) = V(t) + \alpha.\delta(t)$; where $\delta(t) = R(t) - V(t)$

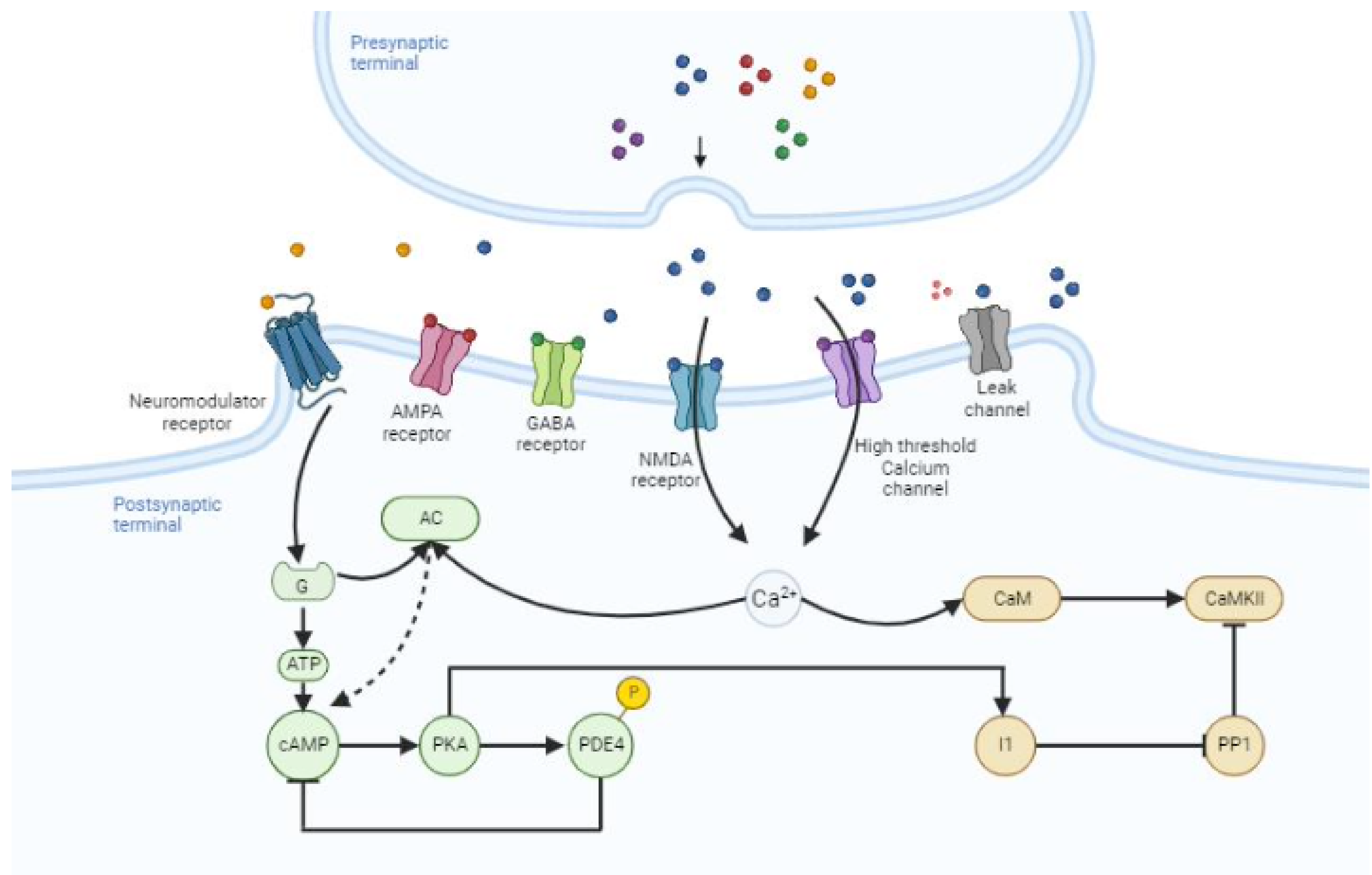
show that in more volatile environments, a larger learning rate α leads to more rewards because it reacts faster to changes. Yet, in more stochastic environments, it is better to decrease α and to ignore noisy evidence. We validated these predictions experimentally in rats [3] and mice [4].





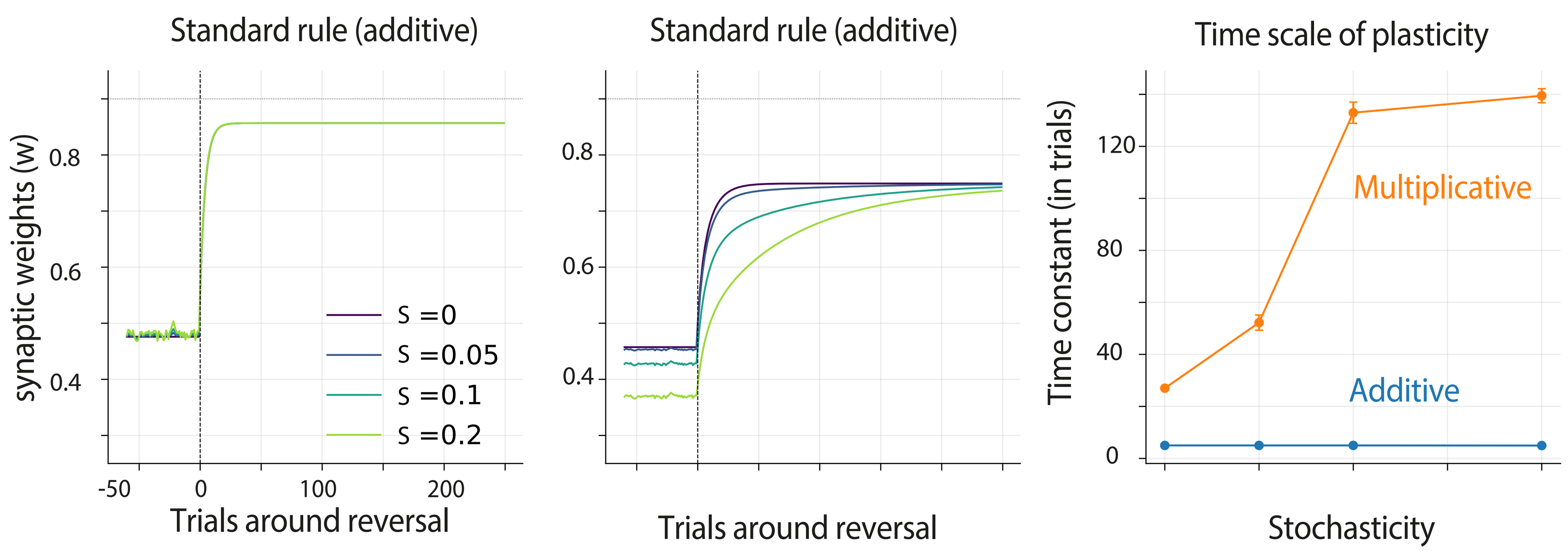
II Biophysical models

Reinforcement learning ultimately emerges from intracellular interactions [2] between the calcium pathway (induced by behaviorally-relevant neuronal activity) and the cAMP pathway (triggered by reward-encoding dopamine). Yet, how volatility and stochasticity relates to these pathways remain totally unown.



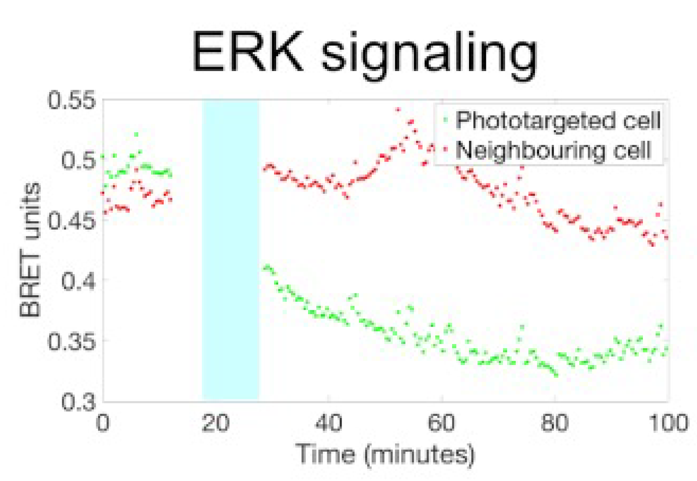
III Bridging the scales

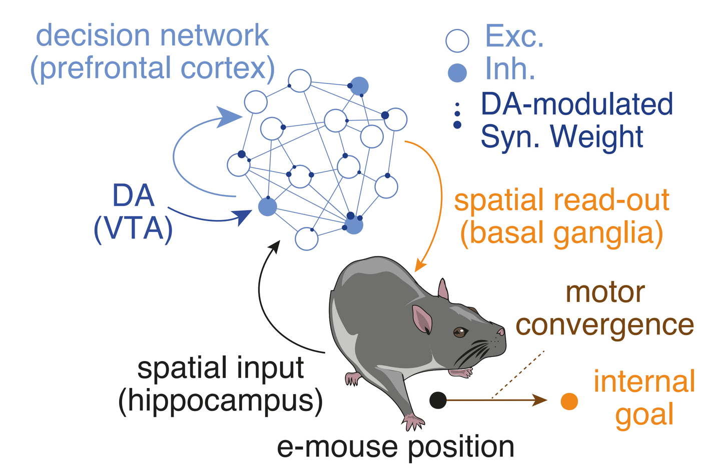
- Standard synaptic plasticity rules (additive) $\Delta m^{\pm} = \alpha[\delta]^{\pm}$
- Candidate : Multiplicative rule $\Delta m^{\pm} = \alpha[\delta]^{\pm}(m_{\max} - m^{\pm})$
- Other mechanisms : negative feedback, cascades, cross-tak



The goal of the internship is to bridge detailed biophysical models (40-50 ODEs) with simplified cognitive ones (2-5 equations) by :
- developing reduced synaptic plasticity models
- including these models in decision network models
- simulating and analyzing their solutions

Perspectives of this work include :
- neural network models [5]
- in vitro test of interactions between pathways using BRET/FRET [6]
- in vivo tests of signaling or neuronal activity during decision task [3]





IV References

[1] Piray, P., Daw, N.D. A model for learning based on the joint estimation of stochasticity and volatility. Nature Comm. (2021).
[2] Maki-Marttunen T. et al. A unified computational model for cortical post-synaptic plasticity. Elife (2020).
[3] Plat et al, Orbitofrontal noradrenaline supports adaptive learning-rate adjustment in probabilistic reversal learning. PNAS (2026) [4] Chevallier et al. in prep.
[5] Naudé, J., et al. Dopamine builds and reveals reward-associated latent behavioral attractors. Nature Comm (2024).
[6] Moutin E. et al. Restoring glutamate receptosome dynamics at synapses rescues autism-like deficits inmice. Mol Psy (2021).