Submission Date: 15 October 2025
Call: October 2025 Deadline
Duration: 48 months

Project Title & Principal Investigator

Principal Investigator
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NeuroDyn

Dynamical Principles of Cortical Network Reconfiguration during Adaptive Sensorimotor Learning

Funding Instrument: Project Funding — Standard
Research Domain: Life Sciences **Panel:** LS5 — Neurosciences

CHF 1 240 000	48 Months	3 PhD + 1 PostDoc	LS5 Panel
Total Budget Requested	Project Duration	Personnel Positions	SNSF Research Area

1. Lay Summary

This summary must be comprehensible to a scientifically literate but non-specialist audience. Maximum 200 words. It will be made publicly available upon project approval.

Every time we reach for a cup, learn a musical instrument, or recover from a stroke, our brain rewires its communication patterns in real time. At the heart of this remarkable flexibility lies the **cortical network**—a web of billions of neurons that reorganize their firing relationships to meet new behavioral demands. Despite decades of research, the precise dynamical principles governing this *reconfiguration* remain poorly understood, in part because existing methods cannot track

rapid network changes at the resolution of individual synapses.

NeuroDyn will develop a unified experimental and computational framework to decode how cortical networks shift between functional *attractor states* during sensorimotor learning. Using high-density silicon-probe recordings in rodents performing a precision-grip task, combined with novel latent-variable models, we will identify the geometric structure of population dynamics that predicts successful skill acquisition. Our results will redefine how adaptive plasticity is conceptualized and open new avenues for brain-machine interface design and neurorehabilitation after motor-cortex injury.

2. Research Plan

2.1 Background and State of the Art

Motor learning requires the coordinated activity of primary motor cortex (M1), premotor cortex (PMC), and parietal areas that together form the **sensorimotor network**. Classical theories characterized learning as strengthening of specific synaptic weights; however, recent population-level recordings have revealed that learning manifests as a shift in the *geometry* of neural trajectories in high-dimensional state space [**?**, **?**].

Two competing frameworks have emerged. The **re-aiming hypothesis** proposes that motor commands arise from the same computational manifold throughout learning, and improvement reflects refined initial conditions. The **manifold expansion hypothesis** holds that the neural subspace itself enlarges as new motor primitives are incorporated. Disambiguating these hypotheses requires simultaneous recordings of hundreds of neurons across multiple cortical regions at millisecond resolution—a capability that only recently became technically feasible with the Neuropixels 2.0 probe family.

Critically, no existing study has tracked *within-session* manifold dynamics at sufficient temporal resolution to capture the moment-to-moment reconfiguration events that precede skill consolidation. **NeuroDyn** addresses this gap directly.

2.2 Specific Aims and Hypotheses

The project is organized around three interlocking aims:

◎ Specific Aims Overview

Aim 1 — Characterize population geometry during learning (Months 1–18)
Hypothesis: As animals transition from naïve to expert performance on the precision-grip task, the intrinsic dimensionality of M1 population activity decreases while trajectory curvature increases, reflecting consolidation of a compact motor primitive.

Aim 2 — Identify causal inter-areal communication modes (Months 12–36)
Hypothesis: Successful trial-by-trial adaptation is preceded by transient increases in directed coherence from PMC to M1 in the beta band (15–30 Hz), reflecting top-down priming of the downstream motor manifold.

Aim 3 — Build and validate a predictive dynamical model (Months 24–48)
Hypothesis: A recurrent switching linear dynamical system (RSLDS) trained on multi-region population data will generalize across animals and predict motor performance from neural population state with greater accuracy than single-region models.

2.3 Methodology

Animal Model and Behavioral Paradigm

Adult Long-Evans rats ($n = 24$, 12 male / 12 female) will be trained on a custom-built *isometric precision-grip apparatus* that requires animals to modulate grip force within a narrow target window (±8% of peak force) to earn a liquid reward. The task is designed to produce a clear learning curve over 10–15 sessions (approximately 3 weeks), enabling repeated within-animal measurement of the same neural circuits across learning stages. All procedures will be conducted under cantonal veterinary license BE-X-2024-1172.

Neural Recording Strategy

Simultaneous multi-region recordings will be performed using two **Neuropixels 2.0** probes (4 shanks, 1280 channels each) chronically implanted in M1 and PMC. This configuration enables stable unit isolation across sessions, which is essential for tracking single-neuron trajectory membership across learning. Spike sorting will be performed with Kilosort 4, followed by manual curation in Phy2. Putative cell-type classification will exploit waveform features and spike-train autocorrelations to separate pyramidal cells from interneurons.

Data Analysis Pipeline

Step 1. **Dimensionality reduction:** Gaussian-process factor analysis (GPFA) will extract smooth population trajectories. We will track the number of dimensions required to explain 90% of variance (*participation ratio*) as a function of learning stage.

Step 2. **Manifold geometry:** Persistent homology (Ripser toolkit) will quantify topological changes in the population activity manifold across learning. Geodesic distances between trial-averaged trajectories will be computed on the learned manifold.

Step 3. **Directed connectivity:** Granger-causal spectral analysis and partial directed coherence will quantify frequency-band-specific directed information flow between M1 and PMC on single-trial timescales.

Step 4. **RSLDS model:** A switching linear dynamical system with $K = 4$ discrete states will be fitted using expectation-maximization with structured variational inference (jax-ssm library). Cross-validated decoding of behavioral variables will serve as the primary model performance metric.

Rigor and Reproducibility

All analysis code will be deposited on a public GitHub repository under a GPLv3 license within 30 days of each manuscript submission. Pre-registration of primary hypotheses will be performed on OSF prior to data collection. Sample size was determined by a power analysis (power = 0.85, $\alpha = 0.05$, two-sided) based on published effect sizes for manifold dimensionality changes in motor cortex (Cohen's $d \approx 0.9$). Data will be stored in the DANDI archive in NWB:N format.

2.4 Work Plan and Timeline

Project Timeline (48 months)

Milestone	Period	Deliverable
Surgeries & rig commissioning	M01–M06	24 animals implanted; rig software validated
Aim 1 data collection	M04–M18	$\geq$ 180 sessions; GPFA pipeline benchmarked
Aim 1 manuscript	M16–M22	Preprint on bioRxiv; code released
Aim 2 data collection	M12–M30	Optogenetic silencing cohort; coherence datasets
Aim 2 manuscript	M28–M36	Peer-reviewed journal submission
RSLDS model development	M24–M40	Open-source Python package (NeuroDynLib v1.0)
Aim 3 manuscript	M38–M46	Submission to *Nature Neuroscience*
Dissemination & archiving	M44–M48	DANDI release; final SNSF report submitted

3. Significance, Innovation, and Translational Relevance

Novelty

- First simultaneous, chronic two-region Neuropixels recordings during a graded motor learning paradigm in rodents
- Application of persistent homology to longitudinal population recordings
- RSLDS framework for multi-region motor dynamics with full open-source release
- Pre-registered, FAIR-compliant data management

Clinical Impact

- Dynamical biomarkers of motor recovery applicable to post-stroke rehabilitation
- RSLDS decoder architecture directly transferable to closed-loop brain-machine interfaces (collaborator: Meridian Neurotech AG, Geneva)
- Mechanistic insight into maladaptive plasticity relevant to dystonia and Parkinson's disease motor symptoms

The proposed work builds directly on the applicant's prior SNSF Ambizione project (grant PZ00P3_201234) in which we established the behavioral paradigm and demonstrated proof-of-concept single-session manifold dimensionality changes in a pilot cohort of 6 animals. NeuroDyn represents a **6-fold scale-up** in animal cohort, a **10-fold increase** in simultaneously recorded neurons, and the first deployment of the topological analysis pipeline in this context.

4. Personnel, Collaborations, and Budget

4.1 Research Team

Project Team

Name	Role	FTE	Responsibilities
Dr. Elena Marchetti	PI	0.50	Scientific leadership, grant management, manuscript writing
Dr. Jonas Wehrli	PostDoc (hired)	1.00	Silicon-probe surgery; neural data analysis pipeline
Ms. Beatriz Ferreira	PhD Student 1	1.00	Aim 1: behavioral training; GPFA analysis
Mr. Luca Ambrosini	PhD Student 2	1.00	Aim 2: optogenetics; coherence analysis
Ms. Anaïs Delacroix	PhD Student 3	1.00	Aim 3: RSLDS modeling; NeuroDynLib software

4.2 Budget Summary

Budget Category	CHF / year	CHF Total (4 yr)
Personnel (PI, PostDoc, 3 PhDs)	267 500	1 070 000
Consumables & animal costs	24 000	96 000
Equipment (Neuropixels probes, optogenetics)	14 000	56 000
Open-access publication charges	2 500	10 000
Travel & conferences	2 000	8 000
Total	**310 000**	**1 240 000**

Budget is calculated according to SNSF salary scales (2025 edition). Personnel costs include employer-side social security contributions (23.5%). Equipment costs are non-recurring; the University of Solaris contributes an in-kind match of CHF 40 000 for shared computing infrastructure (confirmation letter attached as Appendix B).

5. Ethical and Legal Considerations

Animal Welfare

All animal procedures comply with Swiss animal experimentation law (TSchG, SR 455) and cantonal regulations. Experiments have been approved under license BE-X-2024-1172 (Cantonal Veterinary Office, Bern). The 3Rs principles (Replacement, Reduction, Refinement) are central to our design: cohort size is the minimum determined by power analysis, and animals are singly housed only during post-surgical recovery.

Data Governance

No human subjects or personal data are involved. Neural recording data will be stored on University of Solaris encrypted servers (AES-256) during the project, then publicly archived via the DANDI Archive in NWB:N 2.7 format. Analysis code will be deposited on GitHub (GPLv3). All materials will be available within 30 days of manuscript acceptance, consistent with SNSF Open Research Data policy.

6. Applicant's Track Record (Selected)

Selected Publications (last 5 years)

[1] **Marchetti E**, Wehrli J, Fuentes R (2025). Intrinsic dimensionality of motor cortex population activity predicts grip-force variability in rodents. *eLife*, 14:e97423. DOI: 10.7554/eLife.97423

[2] Delacroix A, **Marchetti E** (2024). Recurrent switching linear dynamical systems reveal latent state transitions in premotor cortex. *PLoS Computational Biology*, 20(8): e1012501.

[3] **Marchetti E**, Ambrosini L, Rossi P, Kuebler S (2023). Beta-band coherence between premotor and primary motor cortex scales with motor adaptation demands. *Journal of Neuroscience*, 43(22): 4017–4031.

[4] Ferreira B, **Marchetti E** (2022). A lightweight open-source platform for closed-loop sensorimotor feedback in freely behaving rodents. *Journal of Neuroscience Methods*, 371: 109490.

[5] **Marchetti E** (2021). Manifold geometry of motor learning: a perspective. *Current Opinion in Neurobiology*, 72: 50–57.

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References

[1] Shenoy KV, Sahani M, Churchland MM (2013). Cortical control of arm movements: a dynamical systems perspective. *Annu Rev Neurosci*, 36: 337–359.

[2] Churchland MM, Cunningham JP, Kaufman MT et al. (2012). Neural population dynamics during reaching. *Nature*, 487: 51–56.

[3] Golub MD, Sadtler PT, Oby ER et al. (2018). Learning by neural reassociation. *Nature Neuroscience*, 21: 607–616.

[4] Stringer C, Pachitariu M, Steinmetz N et al. (2019). High-dimensional geometry of population responses in visual cortex. *Nature*, 571: 361–365.

[5] Rouse AG, Schieber MH (2018). Condition-dependent neural dimensions progressively shift during reach to grasp. *Cell Reports*, 25: 3158–3168.

NeuroDyn | SNSF Project Funding Application | Dr. Elena Marchetti, University of Solaris |
Submitted: 15 October 2025 | `e.marchetti@unisolaris.ch`