# MILEDI: Multiscale Modelling of Impaired LEarning in Alzheimer's Disease and Innovative Treatments

**Main area:** Disease modelling and simulation
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## Abstract

Alzheimer's disease (AD) affects over 46 million people worldwide, estimated to triple by the year 2050. It has a long preclinical stage and, before any clinical symptoms appear, pathological processes are observed in the hippocampus and entorhinal cortex, key brain structures responsible for memory encoding and retrieval. AD cannot be prevented, halted or cured today, and new interdisciplinary ways are urgently needed for the understanding and treatment of this devastating disease.

Recent experimental evidence supports the fundamental role of AD-related peptides early in the pathology: in particular the most widely studied Amyloid beta, and the less investigated Amyloid eta and Amyloid precursor protein (APP) C-terminal peptide (AICD). Their differential effects on synaptic function and intrinsic excitability of hippocampal CA1 pyramidal neuron at a single cell level are currently being investigated. However, the dose-dependent impact and complex interaction effects of Amyloid beta, Amyloid eta, AICD on hippocampal synaptic plasticity, CA1 network activity, memory encoding and retrieval capacity and dynamics remain largely unknown.

In this proposal, we will develop a new multi-scale (integrated molecular, cellular and network levels) data-driven in silico model of the hippocampal CA1 region under AD conditions, with the main objectives being: 1) to extend the experimental evidence of Amyloid beta, Amyloid eta, AICD-related changes in the properties of hippocampal CA1 pyramidal neuron synaptic plasticity, synaptic signal integration and neuronal excitability; 2) to incorporate the dose-dependent effects of AD-related peptides into computational models of hippocampal synaptic plasticity, CA1 pyramidal neurons and CA1 network; determine and explain the molecular, synaptic, cellular, network-level mechanisms of altered hippocampal function that leads to impaired learning and progressive irreversible memory loss in AD; 3) to identify and assess experimentally and by computational modeling potential targets for innovative treatment of AD.

The interdisciplinary consortium will perform ex-vivo whole-cell patch clamp electrophysiology recordings (Dr. H. Marie, partner 2-P2), computational modeling of hippocampal synaptic plasticity (Dr. A. Saudargiene, coordinator/partner 1-P1), of neuronal excitability and of biologically realistic large-scale CA1 network (Dr. M. Migliore, partner 3-P3) under control and AD conditions. The consortium has a proven track-record of experimental, theoretical and computational expertise to successfully achieve these goals.

The project extends beyond the state-of-the-art by integrating ex-vivo experimental data into multi-scale in silico approaches to suggest potential targets for more effective treatments in the initial phase of AD. By including the models into the Brain Simulation Platform of the Human Brain Project, the project will provide to the community an essential multi-scale modelling tool for this devastating disease.

## Consortium

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