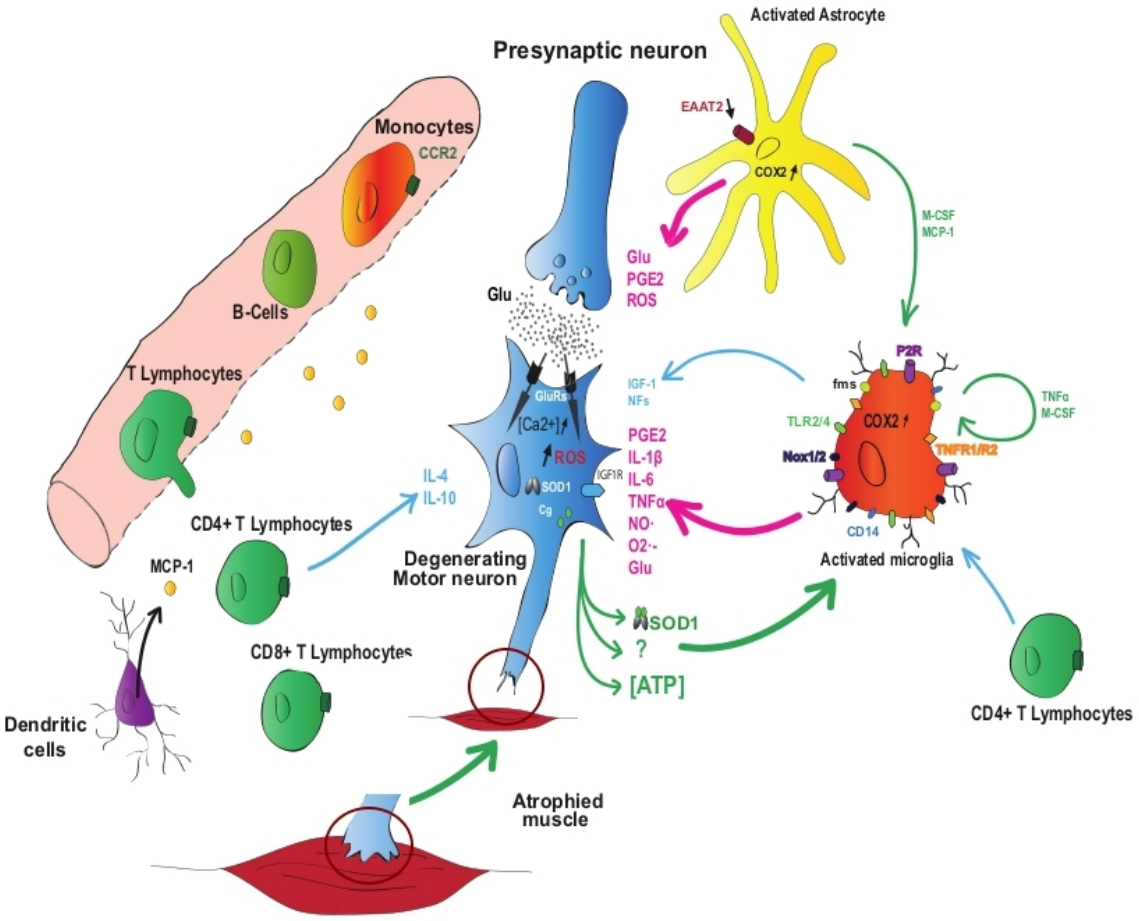
Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease of the adult, characterized by degeneration of motor neurons in the spinal cord, brain stem and motor cortex. Despite the important efforts to find new therapies to ALS, including targeting the immune system, very limited options are available today. This highlights the need to better understand the processes implicated, especially in the progressive phase of the disease to slow down the course of motor neuron degeneration.
Although the cause of the disease is currently unknown, several hypotheses including oxidative stress, protein aggregation, mitochondrial dysfunction, glutamate excitotoxicity and neuro-immune reactions are believed to participate in the motor neuron degenerative process (Boillee et al.2006a). The majority of ALS cases are sporadic, but 10% are inherited (familial), however sporadic and familial ALS produces similar pathological hallmarks, including an immune response in the affected tissues.

In this study, we develop a **mathematical model** of the interactions between astrocytes and neurons during ALS disease course.
This model is available on Github:
https://github.com/Hjertesvikt/ALS_model

Of course, neither the present model nor any other theoretical model can decide between the controversial views put forward by various authors, since only unambiguous experiments can close the debate.
However, mathematical modeling can be a tool to give a coherent and quantitative framework for the discussion, to suggest possible physiological mechanisms and to help plan future experiments.

Despite considerable research and progress, the pathogenesis of amyotrophic lateral sclerosis (ALS) remains poorly understood, in part because of the highly complex and closely related intercellular interactions that occur throughout the pathological process. Therefore, despite the treatment options (Riluzole) to manage and slow the progression of ALS are very limited, and no effective treatment is available.

More and more basic but clinical studies suggest that inflammatory activation of microglia may play an important role during the initiation and progression of the disease. Microglia are innate macrophages resident in the tissues of the central nervous system, they are capable of expressing pro-inflammatory mediators and reactive cellular varieties of oxygen when they are activated by inflammatory signals. In healthy people, if the microglia are at rest it promotes an anti-inflammatory state and this induces the survival of neurons and prevents the proliferation of astroglia.



Amyotrophic Lateral Syndrome

SBML model of immune interactions
Figure adapted from Barbeito and al.

As inflammatory signals develop, microglia can become proinflammatory, leading to the proliferation of astroglia and the death of neurons. Neuronal debris and / or the proliferation of astroglia may in turn exacerbate the inflammatory phenotype of microglia. Knowledge of these multiple positive and negative feedbacks between these different cells is therefore crucial, as these feedbacks significantly alter neuronal structure and function during the pathogenesis of ALS.

Mathematical models can serve as powerful tools for understanding the molecular and cellular processes that control complex diseases. However, there have been few attempts to model the process of amyotrophic lateral sclerosis. Specifically, no systematic approach to modeling using has been reported to examine cross-referencing of the network between microglia, neurons and astroglia, and the corresponding pathological consequences.

Moreover, the modelizations using programs (Java / Python) are difficult to modify and become quickly obsolete simply because of the fast evolution of the computing platforms.

We propose in this evolutionary model, multiple pathways involving many cell varieties, as well as a formalization of intercellular signaling influences. The mechanism is based on the assumption of a constant risk of neuronal death, that is, a single event randomly triggers cell death, regardless of the status of any other neuron, at any time. The spatio-temporal influence of diffusion is neglected because local cellular events are assumed to occur on a slower time scale than the scattering of

signals by chemotaxis. So, in this case, there is no initial event from which the disease develops, but it is very easy to modify this model to look for how a single event could be responsible for initiating the disease.

These metabolic and signaling pathways, link change in each cell population at any time to the values of all cell varieties occurring at that precise moment. For example, the rate of change in surviving neurons is related to the rate of change at resting astroglia, proliferation of astroglia, and pro-inflammatory microglia. At this stage of the modeling, we still use ad hoc biological pathway weights, but during the development of this model, we will gradually replace these arbitrary parameters with equations describing the underlying biology.

The evolution of the cell population in relation to the anti-inflammatory state of microglia is very complex. The evolution of neurons towards neuronal death is irreversible, whereas the evolutions of astroglia and microglia between the resting state, the anti-inflammatory state and the pro-inflammatory state of microglia are reversible.

Compared with other cell types, the proinflammatory population of microglia is highly sensitive to cell-mediated disturbances. Indirectly, this evolution of the population from microglia to the pro-inflammatory state influences the neuronal death which is very sensitive to the amounts of microglia in the anti-inflammatory state. This implies an important role for microglia during the progression of ALS.

Immune cells of the central nervous system, including ***microglia*** and ***T cells***, affect the survival of motor neurons.

In a healthy human, a ***pre-synaptic neuron*** releases ***glutamate*** (Glu), which binds to glutamate receptors (GluRs) on the corresponding ***post-synaptic motor neuron***, causing excitation by the influx of calcium.

Extracellular glutamate is rapidly removed from the synaptic cleft (***Exocytosis***) by ***astrocytes*** through EAAT2 transporters.

In a non-inflamed environment, the microglial cells remain in a state of rest or possibly "of vigilance", presumably ***releasing factors having a neurotrophic influence***.

In the case of an ALS pathology, a ***decrease*** in the expression of the ***astrocyte glutamate EAAT2*** transporters leads to a prolonged excitation of the motoneurons and to participate in their ***degeneration*** (excitotoxic hypothesis).

Activated microglial cells (pro inflammatory) and astrocytes produce toxic factors.

Among the factors released by astrocytes, ***macrophage colony stimulating factor*** (M-CSF) and ***monocyte chemoattractant protein*** (MCP-1) are capable of activating microglial cells by increasing their ***proliferation*** (M-CSF) or their ***migration*** (MCP-1).

Microglial cells are also subject to ***auto-activation*** by releasing tumor necrosis factor-α (TNFα) for which they express receptors 1 and 2 (TNFR 1/2) and M-CSF that act on the fms receptor.

Activated (pro inflammatory) microglial cells will produce more reactive oxygen species (ROS) such as ***nitric oxide*** (NO) via NO synthase and ***superoxide*** (O2-) by activation of ***NADPH oxidases*** (Nox 1/2), but also ***pro-inflammatory cytokines 6 (IL-1β, IL-6)*** and ***prostaglandins*** (PGE2) by activation of ***cyclooxygenase 2 (COX2)***.

Extracellular ATP, probably from damaged motor neurons, binds to microglia purinergic P2 receptors, thereby contributing to microglial activation.

Motor neurons can also participate in glial cell activation by ***releasing mutant SOD1*** co-secreted with chromogranin (Cg) that can bind to CD14 acting in concert with Toll-like receptors (TLR2 / 4).

The adaptive immune system is also part of the degenerative response of motor neurons. T cells (***CD4+ and CD8+***) from the periphery of the spinal cord enter in it during (or even initiating) the inflammatory process of ALS.

CD4+ lymphocytes appear to have a ***neuroprotective*** effect by directly releasing inflammatory factors such as interleukins 4 and 10 ***(IL-4, IL-10)*** or by acting on ***microglial cells to increase their neurotrophic function*** (production of insulin-like growth factor-1 (IGF-1)) .

The role of infiltrating CD8+ T cells remains undetermined and B cells are not present in the spinal cord.

Dendritic cells (antigen-presenting cells) secrete ***MCP-1***, which probably participates in the infiltration of peripheral immune cells.

Overall, the inflammatory environment and increased oxidative stress contribute to the degeneration of motor neurons, resulting in muscle atrophy of ALS.