# Data driven control and machine learning to induce cell reprogramming by using mechanobiology framework

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**Abstract**

Living cells are constantly exposed to mechanical stimuli arising from the surrounding extracellular matrix (ECM) or from neighbouring cells. Mechanical forces acting on cells are well known to induce intracellular biochemical signals, which play important roles in cellular behaviours such as proliferation, growth, migration and differentiation. [1] Cells' ability to sense the mechanical stimuli is referred as mechanosensing.

External forces applied to a cell are transmitted via the cytoskeleton to the nucleus, resulting in (intra-)nuclear deformations: these deformations could alter the organization of DNA inside the nucleus [2].

The growing evidence supporting the crucial role of the nucleus in mechano-sensing has promoted the development of experimental tools to detect cell responses to controlled and finely tuned physical stimuli, thus allowing functional dissection of the mechano-transduction processes.

In particular, in a typical in vitro stretching experiment, cells are cultured on thin, elastic, transparent substrates coated with extracellular matrix molecules to promote cell spreading and adhesion. Then, mechanical stress is applied by using an actuator called cell-stretcher. Such device applies a deformation to substrate that is transferred to the cell through the interaction of cellular adhesion protein and ECM ones. Uniform uniaxial or biaxial strain is subsequently applied to the substrate while monitoring on a microscope the cellular response before, during, and after strain application.

At the state of art, the "dosage" of mechanical forces is set by the user on the base of its (partial) knowledge of the system and of the desired output since an analytic relationship between stress and cell-mechanosensing is not yet available. As a matter of fact, such phenomena seem to be highly stochastic and based on a large set of experimental condition variable.

The aim of this PhD thesis is the development of an automatic closed-loop control system to regulate mechano-sensing activities, capable to automatically grasp the correlation between variables and exploit them to achieve the user's goal. Because of the limited knowledge of the environment, the controller cannot be a standard model-based one; as a matter of fact, to accomplish its task, the controller has to interact with the cellular environment by using a set of optimized trial and error algorithms, typical of the new data-driven control discipline.

The control system will be composed of two layers, hereafter reported as "low level control" and high-level control". The high-level control tries to make hypothesis about correlation among variables. The low-level subsystem evaluates the hypothesis by interacting with the environment and gives signals back to the previous layer about confirming or rejecting the tested hypothesis.

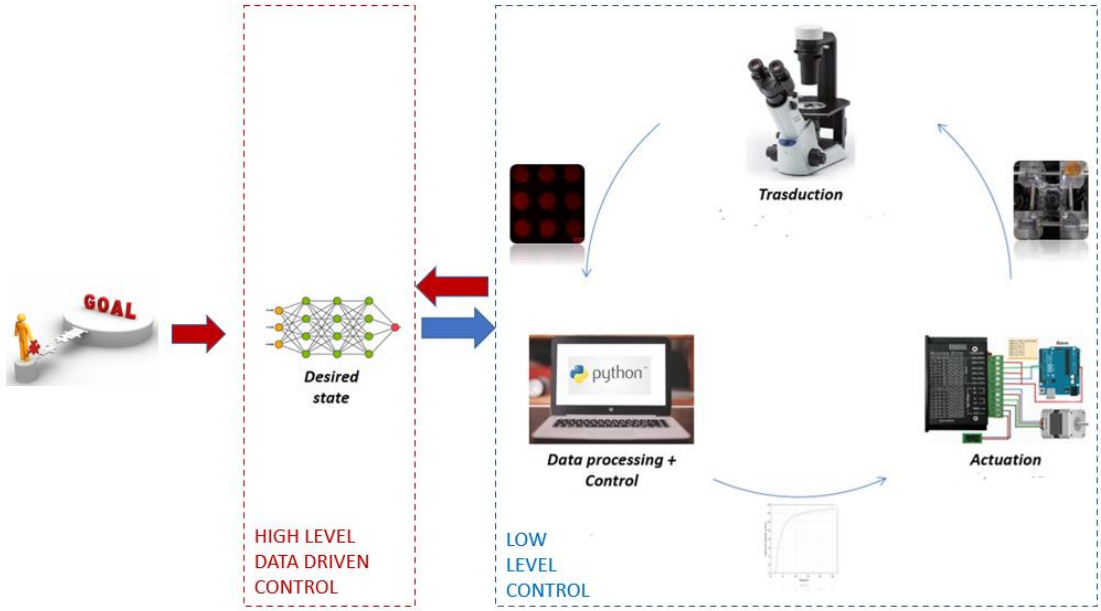


*Figure 1: Structure of the automatic control system: the high- level data driven control try to find hidden relationship among data by interacting with the cellular environment. The low-level control subsystem execute the command from the previous layer and gives back signal.*

[1] Martino F, Perestrelo AR, Vinarský V, Pagliari S, Forte G. Cellular Mechanotransduction: From Tension to Function. Front Physiol. 2018 Jul 5;9:824. doi: 10.3389/fphys.2018.00824. PMID: 30026699; PMCID: PMC6041413.

[2] Isermann P, Lammerding J. Nuclear mechanics and mechanotransduction in health and disease. Curr Biol. 2013 Dec 16;23(24):R1113-21. doi: 10.1016/j.cub.2013.11.009. PMID: 24355792; PMCID: PMC3883624.

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