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Sciences **M**écaniques, **A**coustique, **E**lectronique, **R**obotique

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Laboratory : ISIR

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Title of the thesis: Microrobotics Toolbox for Experimental biology

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Résumé en français

Ce projet vise à développer des techniques robotiques spécialement adaptés aux cas des expérimentations en électrophysiologie. Il s'agira de donner la possibilité aux expérimentateurs de facilement mettre en place un scénario de mesure et d'analyse sur des échantillons comportant un nombre important des neurones, dans une variété de contextes (cultures, tranches, rétine isolée). En effet, ces types d'expériences sont pratiqués sur des échantillons très complexes et il est actuellement impossible pour une machine d'une part de détecter la zone d'intérêt d'une cellule inclus dans le tissu étudié, et de l'autre de guider l'outil de mesure avec une précision micrométrique en utilisant uniquement l'image du microscope optique. En utilisant les méthodes de commande issue de la robotique moderne, nous visons à développer un superviseur intelligent qui sera capable des performances similaire à un expérimentateur humain. Il sera donc possible d'augmenter considérablement l'efficacité des expériences et augmenter leur rendement.
L'objectif est de produire des données expérimentales en grande nombre sur le comportement des neurones, sous l'action des divers stimuli qui alimenteront des bases de données et des modèles phénoménologiques.

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Context

Experimental studies in biology are a major source of novel advances. Also, automation has been an important part of biomedical research for decades, and the use of automated and robotic systems is now standard for such tasks as DNA sequencing, microfluidics, and high-throughput screening. However, current penetration of robotic techniques into biomedical laboratories is relatively low, and revolves around considerably simple use cases and rudimentary interfaces. Especially in cases where access to a single specimen such as an isolated cell, a neuron or bacteria is required for example for probing or stimulation, motorized micromanipulation equipment generally replaced manual vernier based systems. However, the interfaces barely shifted from verniers to an electronic console where the operator still controls different degrees of freedom independently, very much like the manual case. This limitation comes from the fact that every higher level implementation of automation reduces the flexibility of the experimental setup. As a matter of fact, the specimens, tools and experimental environment may differ greatly even between similar experiments. For a biomedical experimenter without firm skills in engineering and robotics it's extremely difficult to conceive and implement a robust automation scheme and straightforward full manual operation remains the most time-effective and flexible approach. However, there is clearly a huge potential gain in the ability to repeat an experimental task in great numbers because statistical studies are the main approach to elucidate most biological processes.

There is currently considerable effort to increase the impact of robotics and automation in biologic research. Several tasks like cell injections and neuron patch-clamping are identified and has been the object of several successful implementations, albeit with severe limitations. Most works has concentrated on a limited part of a full experimental task: trajectory control of micromanipulators (Wu et al., 2016) ; automated pressure control (Kodandaramaiah et al., 2012) ; using game controllers as a user-interface (Perin and Markram, 2013); coupling pressure and electric measurements (Kodandaramaiah et al., 2016) ; pipette cleaning (Kolb et al., 2016). The most advanced implementation, blind patch-clamping (Desai et al 2015), is in fact quite simple from a robotics point of view because it involves no target selection and single axis motion. Most of these works are based on basic robotics concepts, as they implement some form of closed loop control or elementary user interface paradigms.

Objectives

The advantages of implementing robotic technologies for experimental biology are now well established. There is however still an important gap to put this technology in the hands of laboratory technicians, whose training obviously didn't include robotics or control. There isn't also any 'one size-fits-all' robotic recipe which can be used in any experimental setup.

The objective of this work is to provide an intermediate automation toolbox, with a straightforward and intuitive interface. It would allow the operator to implement an automated scenario for a given experiment though an intuitive graphical interface, by combining trajectory control, image processing, different sensory inputs or other devices such as pressure controllers, input devices, or virtual reconstruction of samples and experimental setups. The flexibility of the system is effectively the key to its success: commercial solutions exist today but they are quite specific to a single application and encompass both the hardware and the software. Our aim on the contrary is to produce a software library, which can be implemented on various hardwares generally found on experimental setups, and with great flexibility.

Recent years have seen considerable progress around ROS for classical robotics. We strive to develop a similar framework but adapted to special case of experimental biology, hence involving a much tighter list of components but with specific control issues, and a higher level user interface, designed with the specificities of our target audience in mind.

An important aspect of the problem is the robustness over variability of robotic structures. Our initial works (2 master internship projects) have been instrumental to show the limitations of simple control approaches as the imprecision on the identification of kinematic structures, mechanical noise, friction and hysteresis on joints are important sources of lack of repeatability and clearly calls for advances techniques. On the other hand, this complexity should be hidden to the end-user. Our proposed approach is to first establish a list of elementary tasks, which will be implemented with a high robustness, using eventually cross calibration and hybrid control techniques. A simulink-like interface will be investigated to let the users handle the system. Other interaction approaches like show-to-teach or inline learning can be later explored.

In close collaboration with *Equipe Neurosciences computationnelles des systèmes sensoriels* we aim rapidly to proceed experimentally and investigate two experimental cases. The first one is patch-clamp, mentioned above, where a pipette carrying an electrode should be inserted inside the cell body of a neuron, or its axon. This operation requires 10 to 30µm of precision for the cell body and 1µm for the axon. The objective is to let an operator assemble a scenario where the system can autonomously perform measurements on a big number of samples. This operation has several issues barring its automation: the controller provided with current actuators doesn't provide this repeatability, although the hardware itself is capable; samples, and the pipette are actually deformable elements, as such actuator position feedback does not relate to end-effector positions; optical microscope feedback is poor and limited to 2D; pressure control is extremely variable depending on the pipette and the sample cells…

The second experimental scenario concerns the measurements on untethered organisms, such as floating cells or unicellular organisms such as ***Paramecium***. Commonly studied as a representative of the ciliate group, Paramecia are readily cultivated and easily induced to conjugate and divide and has been widely used in classrooms and laboratories to study biological processes. Such experiments are currently conducted by capturing manually a single specimen, then immobilizing it before making measurements or micro-injections. An interesting approach would be to develop a virtual immersion chamber for such a specimen, with adapted microfluidic flow control and chemical inputs. This 'virtual reality' would open brand new opportunities for experimental studies

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