Robine
Robotics for Correlarive Microscopy

Open position for PhD thesis in robotics and control

Title:	Design and Control of a High Speed Poly-Articulated Micro-Robotic System For Correlative Microscopy
Hosting Laboratory:	Institut des Systèmes Intelligents et de Robotique, CNRS UMR 7222, Sorbonne University Team: multiscale interactions
Address:	4 Place Jussieu, CC 173, Pyramide - T55/65, 75005 Paris
Partners:	- The University of Newcastle, Australia - Centre de recherche en Myologie (UMRS 974), la Pitié-Salpêtrière hospital, Paris
Duration:	3 years
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Project:	ANR JCJC Robine
Application deadline	June 3, 2020
Starting date:	October 2020

1- Context

The world of micro-scale objects is much more interesting when you know what you are looking at. This is what we are targeting with Robine project that aims at developing a robotic system able to achieve correlative microscopy in the word of the small scales, from the millimeter down to the size of individual atoms.

We are working within a micro-robotics research team at ISIR and collaborating with the best robotics laboratories in France and over the world for a common goal: extending the capabilities of robots for a better understanding of what it happens in the world where objects are invisible to the naked eye. In particular, our proximity with AP-HP, Pasteur and Curie Institutes, already partners of our team, offers a unique network to lead research activities in microrobotics for medical and biological applications.

What is micro-robotics?

In his famous lecture [Feynman 1960], Richard Feynman, Nobel Prize in Physics 1965, has inspired a whole generation of scientists who have dedicated their career to explore the word of small scales, from the millimeter down to the size of individual atoms.

"*What I want to talk about is the problem of manipulating and controlling things on a small scale*" R. Feynman.

Since then, progress in robotics has dramatically extended the ability to explore, observe, feel, understand, and manipulate a variety of samples at the small scales. The field of micro-robotics "covers the robotic manipulation of objects with dimensions in the millimeter to micron range as well as the design and fabrication of autonomous robotic agents that fall within this size range" [Nelson et al. 2008]. **A micro-robotic system has not necessary dimensions at the micro-scale** but it uses end effectors that can manipulate, characterize and observe micrometer sized objects. **Theory and techniques established for robotics can be applied to micro-robotics** and new paradigms have been also considered to extend the capabilities of robotic systems to deal with the specificities of the small scales.

How a micro-robot can be used as a microscope?

The elementary microscope involving a micro-robotic system is the Atomic Force Microscope (AFM). Introduced for the first time by Gerd Binnig and his colleagues at the IBM Zurich Research Laboratory [Binnig et al. 1986], the AFM has been the basis for the development of microscopy technics to form an image of a sample surface in the three-dimensional shape (i.e. topography) at a resolution on the order of fractions of a nanometer.

The basic working principle of an AFM consists in using a probe[1] able to detect and measure interaction forces acting between its tip and the surface of a sample at a very short probe-sample distance. In its original form, a micro-robotic system is used to either move the probe or the sample holder in X, Y and Z directions. The X and Y degrees of freedom of the microrobotic system are used to scan the probe along the sample surface. When a variation of the interaction force is detected by the probe due to the sample topography, the Z-axis displacement is controlled in order to keep the force at a constant value and therefore to keep the probe-sample distance constant. X, Y and Z position measurements of the microrobotic system recorded during the scanning process are then extracted and used to build the topography image of the scanned sample. To obtain a complete "map" of the measured sample property like topography, the scanning has to be done in a controlled way. Hence, a classical AFM relies mainly on the ability to perform an efficient **closed loop force and position control of the microrobotic system.**

The AFM is a fundamental observation and manipulation tool at the micro and nano-scales for several applications in material science, biology and medicine.

2- *High speed AFM and 3D AFM:* ***challenges for robotics and automatic control***

While it has allowed the observation of the atom itself, there is yet a yearning for AFM to be made faster, able to follow sudden changes of a surface topography in vertical undulations, and capable of automated implementations. All of which are the subject of increasingly pointed research.

Scan speed: It depends mainly on the micro-robotic system motion speed (bandwidth of each DOF), the probe resonance frequency and electronics circuits. The design and the control of High-Speed (HS) flexure guided nano-positioners for AFM applications, has been an important filed of research over the past two decades [Yong et al. 2012] [Bazaei et al. 2019]. These structures are designed to provide high bandwidth dynamics in X, Y and Z motion directions (from the kHz to the MHz) of the micro-robotic system to allow the AFM tip to

[1] Usually a micrometer sized cantilever with a sharp tip used as a force sensor.

hover over the entire sample as fast as possible. HS-AFM have opened the way for a direct observation through video AFM of several dynamic phenomena at the molecular level, which is yet not possible with other microscopy technics. In the stat of the art, one of the fasters HS-AFM can image proteins at 10-20 fps [Ando et al., 2018].

"Real" 3D-AFM: - ***3-DOF XYZ micro-robotic system not enough? Orientation control needed? Observability and controllability issues? -*** With classical AFM, the scanned sample image could be distorted due to the orthogonal scan configuration and the probe tip geometries especially when the sample presents steep sidewalls. In 3-D AFM, the probe tip or the sample should be configured in a way to sense the detailed topography around the sidewalls for a higher resolution and a more detailed topography reconstruction. Much research has been done to refine the AFM measurements along the sidewalls and to resolve the corner's image distortion [Xie et al., 2016]. To improve the AFM image quality at the sidewalls of the scanned sample, multi-DOF control of AFM based micro-robotic systems during the scanning process is an open research topic.

Correlative microscopy: - ***team work for a better data acquisition-*** Correlative microscopy merges the best capabilities of two or more microscopy technics toward new ways of nano-structures observation. In the case of AFM, the micro-robotic system can operate inside a light microscopes (LM) or an electron microscope (EM). LM or EM can be used to define regions of interest where the AFM can operate [Liang et al. 2019] [Liang et al. 2020]. Hence, the AFM will operate only in these regions and will provide additional informations such as dimensional, topographic or biophysical data of a sample. In correlative microscopy, images obtained with electron microscopes or light microscopes can be combined with those obtained with AFM.

3- *Objectives of the thesis*

3.1- *Research topics*

The thesis presents several scientific challenges related to poly-articulated micro-robotic systems design for scanning probe microscopy at video-rate, to their modeling and to their closed loop control for high speed 3D scanning in a correlative microscopy context. More details will be given during the interview.

Prototypes of AFM based micro-robotic systems available at ISIR can be used as a starting point [Acosta et al. 2013] [Abrahamians et al. 2013] [Boudaoud et al. 2018] [Cailliez et al. 2020].

3.2- *Medical context*

To demonstrate the usefulness of the approach, we target one application area related to the dual AFM microscopy in a correlative way with an electron microscope or with a light microscope, to analyze intracellular structures of muscular cells suffering from neuromuscular disease called centronuclear myopathy (CNM). We particularly target the issue of diagnosis of diseased cells by a precise reconstruction of the overall 3D shape of nanostructures with a typical size between 10 nm and 500 nm. In particular, a precise 3D rending of the clathrin protein is of primary importance since its role in the myopathy has been demonstrated [Vassilopoulos et al. 2014]. Such a microscopy involving small scale robotics will allow a fast differentiation and discernment of different types of intracellular structures, will provide precise dimensional informations of such structures and will push forward the understanding of myopathy mechanism. For that purpose, a direct collaboration will be conducted with the Institute of Myology inside the hospital La Pitié-Salpêtrière is Paris which is a partner of the project Robine. Collaboration with the University of Newcastle, Australia, with which we have done preliminary works on the design of a micro-robotic high speed AFM stage [Bazaei et al. 2019] will be conducted.

4- Hosting laboratory

The Institute for Intelligent Systems and Robotics (ISIR) is a leading laboratory in robotics that brings together researchers and academics from different disciplines of engineering sciences, information and life sciences. Located in the Quartier latin, Paris, the ISIR is a joint research laboratory (UMR7222) which belongs to Sorbonne University and the Centre National de la Recherche Scientifique (CNRS). Gathered in 5 multidisciplinary teams, research activities of ISIR address major societal challenges for health, industry of the future, transport and personal service where robotics plays a central role. The "multiscale interactions" team at ISIR conducts research activities in microrobotics, automatic control, haptics and human–computer interaction (HCI). For micro-robotics and control activities, the team hosts 100 m2 of experimental rooms with facilities at the cutting edge of technology. ISIR is one of the two labs in France that host experimental platforms of *Microrobotex* from the robotics French governmental program "investissement d'avenir".

5- Qualifications required

- We are seeking a motivated candidate with a solid background in robotics and/or mechatronics and/or control. A preliminary knowledge in the field of micro-robotics is not required.

The selected candidate will have the opportunity to handle an exciting researcher subject that has the potential to extend the knowledge in robotics and control and to provide a new robotic instrument for advanced microscopy with a promising application in biology and medicine. The candidate will take advantage of the long experience of the micro-robotics team of ISIR in this field.

6- How to apply

The candidates should send a detailed CV, a motivation letter, transcripts (master's degree or equivalent) and contact informations (name, institution, email address) of two referees. The documents must be sent before June 3, 2020, in a zipped format to
mokrane.boudaoud@sorbonne-universite.fr

7- References

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