Challenges in Robotics toward Cyber-enabled Multi-scale Multi-paradigm Life Science Automation

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This roadmapping input proposal addresses major challenges faced by the highly interdisciplinary and fast emerging robotics-related area of life science automation. The focus is on robotics related to multi-scale and multi-paradigm life science automation needs. Multi-scale means from macroscale, mesoscale, to nanoscale. Multi-paradigm means from software to hardware, specifically from control software, automation process data-driven information management software, to robotic system automation involving sensors and integrated advanced bio-instrumentation. We suggest the following research challenges as being indicative of the key roadmapping issues in life science automation:

1). Scanning Probe Microscopy (SPM) Augmented Robots for High Throughput Multi-scale Bio-manipulation. To automate *in vivo* single-cell surgery or manipulation, a robot needs not only to be as precise as the atomic force microscopy (AFM), but must also have maneuverability suitable for non-flat surfaces and moving targets. This challenge requires the development of scanning probe microscopy augmented with integral bio-manipulation robots that can efficiently move at the macroscale (the robots) and simultaneously move at nano-scale (the SPM). The robotic system should not be viewed as a single SPM integration with a robot, but organic integration of multiple various SPM components (AFM, STM, and NSOM) or other nano-scale tools into an integrated robotic framework. This general idea is currently beyond the state of the art in SPM and robotics. One example is a biological atomic force microscopy and laser scanning con-focal microscopy (LSCM) integrated robotic system that the authors are currently working on. The AFM and LSCM integrated system can be operated simultaneously to investigate cell surface morphology and the cell internal dynamics. The system can be used for high throughput single cell manipulation and imaging. Intelligent control concepts will be used such that this system will be able to track dynamic targets of interests. Robotics researchers must understand internal dynamics of the biological cellular system, and utilize the information for the SPM augmented bio-manipulation robot system control to achieve the desired functionality. It is believed that new challenges are ahead in dealing with the dynamic coordinate transformations for this class of multi-scale systems. The systems engineering challenges across the spectrum of control software and hardware automation in such systems are believed to be critical enabling technology factors.

2). Bio-manufacturing robots with flexible interfaces for multi-scale biological material handling. Robots will continue to play an increasingly important role in genomics and proteomics research. To date, they have been used mainly for biological material handling. However, applications are limited due to lack of flexible interfaces that facilitate efficient implementation and integration with the multitudes of biological materials and material holders. Most current robots used are adapted from semi-conductor manufacturing, which were originally developed for wafer handling. In life science automation, biological materials being handled can be in liquid, solid or even gas forms. The material holders can be bottles, micro titer-trays, multi-well plates, cassettes or multi-liter volume containers. The information/data dealt with is often quite large and multi-scale, and may include DNA and protein microarray data, or large scale biological organism information. To ensure accuracy and improve throughput, robots with computational intelligence and flexible interfaces are essential. An example is to have one or a few robots assisting in a work cell that includes DNA/protein microarray fabrication cells, or high throughput drug screening stations. The robot is expected to be intelligent enough to automatically adjust its information interfaces to accommodate different scales of data. In addition, such bio-manufacturing robot systems must be accurate and utilize vision-based control, while minimizing human interactions. In nano-scale manipulation, virtual environments will be required to create effective human-machine interfaces. Interfaces between the multi-scale operations and multi-paradigm implementations are difficult to achieve efficiently. This remains an open automation area to be addressed from the robotics point of view. New engineering methods, tools and techniques are needed. Finally, bio-manufacturing robots are often expected to manipulate, or deposit, biological objects/materials with high location accuracy, volumetric and gravimetric precision, and at high throughputs. Such requirements are critical in dealing with high-volume complex date and interacting with external systems. There are many complex internal feedback processes that must be studied at scales that are much different than processes occurring in nature. We need to intersect with computational and physical as well as biological worlds to address such challenges. Essentially, we are proposing independent computational intelligent robots that can physically deal with biological materials flow for handling multi-scale biological data in pharmaceutical or biotech manufacturing industrial applications. Clearly, conventional robots can not meet such requirements. Investigations into the cyber-enabled multi-scale multi-paradigm life science automation framework are foundational toward achieving comprehensive automation. These advances associated pharmaceutical and biotech industry will eventually lead to dramatically lower costs in the life sciences and associated industries.

The above new concepts and tools, although specific, are central to research at the frontier of life science automation. Corresponding impacts to robotics and computational discovery in education, and workforce development for the 21st century are significant and broad.