2016 American Control Conference (ACC)
Boston Marriott Copley Place
July 6-8, 2016. Boston, MA, USA

Control on a Molecular Scale: a Perspective

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***Abstract*— Imaging and manipulating objects down to the molecular level plays a crucial role in many disciplines. It allows to unravel molecular phenomena, to form materials with new chemical and physical properties, or to build objects on an atomic scale. Science on the nanoscale is inherently interdisciplinary. It requires knowledge and insight into many fields, spanning from modeling, measuring, imaging, actuation to control. Often feedback control facilitates operation with molecular precision, despite the fact that many physical phenomena at the molecular level are still not well understood, and that stochastic and nonlinear effects are inherently present. This work provides an insight into some of the current control related research activities on a molecular scale. This is done considering examples from different fields: control related to scanning probe microscopy such as atomic force microscopy, controlled self assembly on a molecular scale, control aspects of molecular transport, and the use of control for manipulation of single molecules using macroscopic probe tips. The hope is that control related researchers, who are not experts in these fields, become aware of the opportunities present, which could also drive new theoretical developments.**

I. Introduction

Manipulating and understanding matter at a scale of hundreds of nanometers down to a few nanometers – nanotechnology and science – plays an important role in many disciplines and applications [1]. In the 1980s Eric Drexler [2] helped bringing the term nanotechnology into the vocabulary of the general public, and it is now a large, scientifically and commercially active field. Applications of nanoscale technology span from new materials, electronics on a molecular level to new sensors in biotechnology and cancer treatment, c.f. [3], [4], [5], [6] and references therein.

The idea of nanotechnology was probably first introduced by Richard Feynman in his 1959 speech entitled "Plenty of Room at the Bottom" [7].

> "I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle ... What I want to talk about is the problem of manipulating and controlling things on a small scale."

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While Feynman may not have been explicitly referring to it, feedback control, dynamic modeling, and optimization have become invaluable tools to measure on an atomic and to manipulate matter on microscopic and even nanoscopic scales.

A. Feedback and molecular imaging and manipulation

Feedback plays an important role when working on the nano level: stochastic phenomena dominate at small length scales. Furthermore, systems at that scale are often extremely sensitive to initial and environmental conditions, such as temperature, humidity, and pressure. Nanoscale phenomena are completely different in characteristics than macroscale ones [8]. Often weight and inertia forces are negligible, while interatomic forces, surface chemistry, contact mechanics, which are often not completely understood at this scale, are dominant. Strong nonlinearities are present, which increase significantly if atoms come close. Control, even very simple approaches, allow to reject disturbances and account for unknown or not well understood phenomena, thus allowing to achieve precise imaging or manipulation. Despite the fact that feedback can confer the required robustness and has lead to significant improvements in todays nanotechnology [9], [10], there are still many practical and methodological challenges before control at the molecular scale becomes pervasive.

At the time of Feynman's speech the possibilities to interact – measure and actuate – at small length scales were limited. Today, approaches such as atomic force microscopes (AFM) and scanning tunneling microscopes (STM), which allow imaging down to the atomic level are now widely used, c.f. [11], [10], [12], [9], [13]. Many of these imaging techniques follow the basic principle of scanning probe microscopy (SPM), see Fig. 1, introduced by Binnig and Rohrer in [14]. A probe, typically a sharp tip, that can be moved in (x, y, z), e.g. by piezo elements, is scanned over a surface at very short distance. For imaging purpose, a particular property of the tip-surface junction (typically conductivity or acting force) is either mapped directly or it is used as input into a feedback loop that keeps this property constant during image acquisition. Such images are therefore "iso-property" images. Control in such devices is present at multiple levels: It often is required to guarantee the iso-property; to move the actuators, i.e. the piezo elements with the required precision: to compensate disturbances/noise due to temperature variation; or to compensate vibrations. While these imaging techniques are widely available and of huge

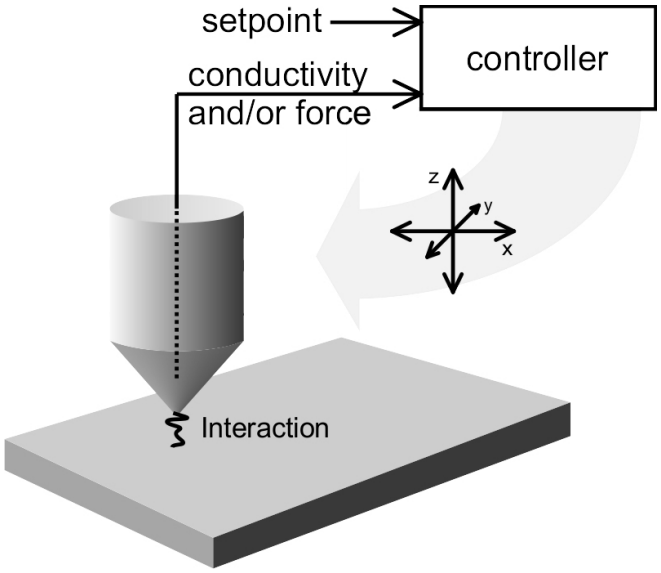

Fig. 1. Basic principle of scanning probe microscopy. A sharp probe is scanned over a surface, mapping either properties such as conductivity or force, or the input required to keep these properties constant at a given set point.

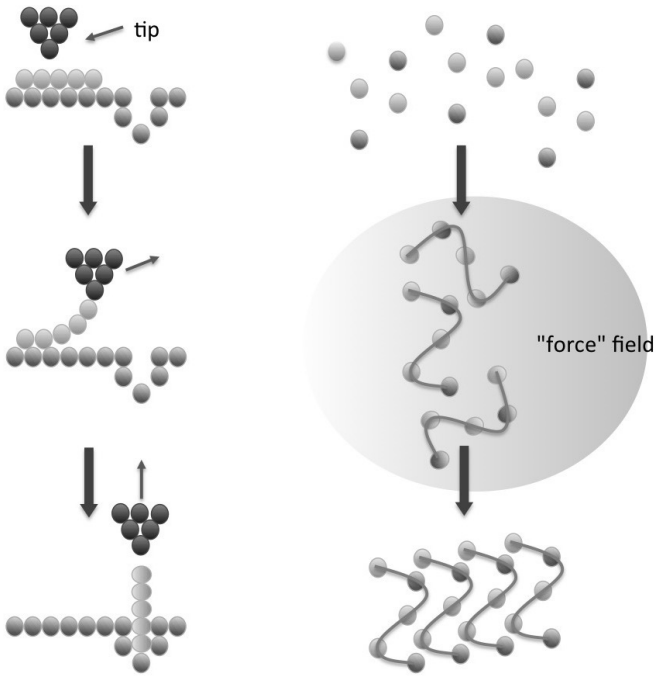

Fig. 2. (left) Example for molecular manipulation using a SPM tip. The probe approaches the molecule and binds due to atomic forces. The molecule is lifted up and placed by the tip. (right) Example for self assembly. Small molecules react and form a complex molecule. These molecules then self assemble/self organize. The process might be controlled by external "force" fields, e.g. ultrasonic waves, magnetic fields.

value in many fields, it is important to note that they are often not easy to handle nor to use in a routine way [15], [11].

With respect to "actuation" on a molecular level, multiple approaches are also available by now [12], [9], [16], [5], spanning from SPM-based approaches, self organization and assembly based approaches, to optical and magnetic tweezers. One typically distinguishes between approaches based on (see Fig. 2)

- *self assembly [16], [17]*, in which external fields influence a possibly large number of components/molecules, such that they orientate and align in a desired way and form chemical bonds.
- *molecular manipulation [18], [10], [19]*, in which only a small number of components are directly actuated.

The dynamics of small-scale systems are typically high-dimensional, nonlinear, stochastic, and show time scales in the order of nano- and microseconds. This challenges approaches for modeling and simulation, which play an important role in understanding the underlying phenomena. As a consequence, interacting with the systems in a structured way becomes more difficult. However, advances in computation, modeling, and simulation over the past fifty years have made simulation over multiple scales, from the molecular to the macroscopic level, possible [20], [21].

Despite these advances it is important to realize that actuation, sensing, modeling and simulation are still limited, relative to the often high dimensionality of the underlying collection of atoms. Furthermore, the technologies for imaging, and especially manipulation and controlled self-organization are still in their infancies and are not yet widely applicable.

B. Structure and objective

The area of control on a molecular level is extremely broad and heterogeneous, just as the control problems in aerospace engineering or chemical engineering are manifold with their own unique challenges. We aim to provide control researchers with an understanding of the key distinctions in the field, such as the difference between self assembly versus molecular manipulation. We outline some of the open questions and possible research directions. We do so by considering examples from different fields. By this we hope to make the control related researchers who are not experts in these fields aware of the opportunities to apply their expertise in certain applications of molecular control. To provide a complete and comprehensive review of the field of control on a molecular level, is neither possible, nor the aim of this work. We rather provide some personal insights and perspectives. Furthermore we hope that by presenting the work in the context of a control loop: actuator-process-sensor-controller, the details of the molecular science should be accessible to control researchers who are not experts in this application area.

The remainder of the paper is structured as follows: In Section II we touch on the issue of efficiently modeling and simulating over multiple time scales, taking a control perspective to couple the different scales. Section III outlines the control and the integrated design of probe based imaging devices, considering atomic force microscopy. Controlled self assembly, molecular manipulation and control related to

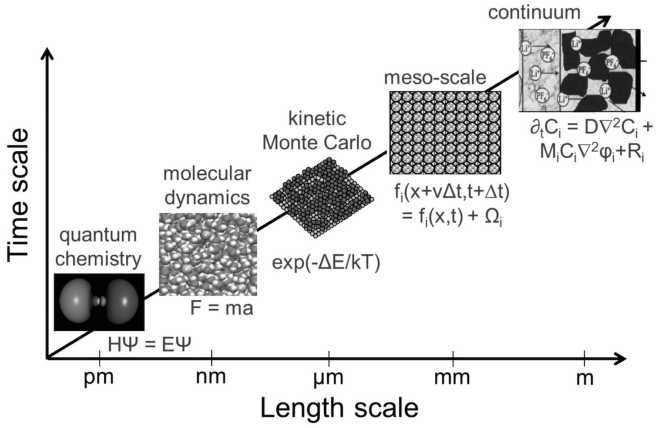

Fig. 3. Illustration of different simulation model types as a function of the length and time scale of important/relevant phenomena.

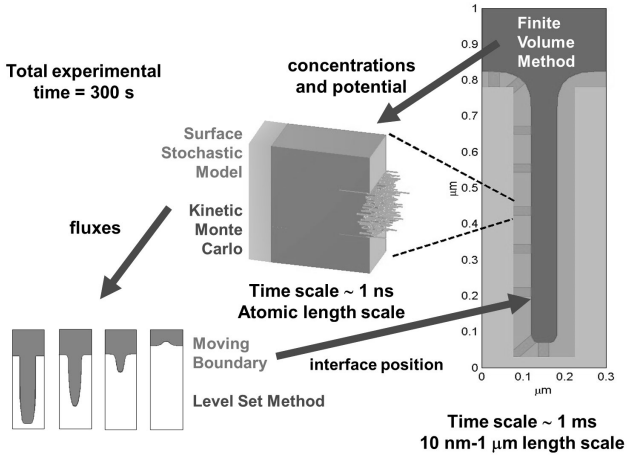

Fig. 4. Dynamic coupling of multiple simulation models of different time and length scales for the electrode position of copper within a trench to form a copper interconnect in a microelectronic device [26].

transport on a molecular scale are considered in Section IV, before closing in Section V with a perspective towards control and systems challenges in the field of controlled molecular manipulation.

II. Multiscale simulation and modeling: connecting different scales in time and space

As for molecular systems (online) sensing capabilities are usually limited, models are often needed to shed light and unravel the underlying principles. Furthermore, they often form the base for the optimal design of the process and the control/imaging system on a molecular level. Many molecular systems are coupled to phenomena that are dominant over large spatial domains, which means that often the molecular models over small spatial domains need to be coupled to macroscopic models over large spatial domains – such models are referred to in the literature as *multiscale models*. Multiscale models and their simulation is often one of the time-consuming steps in understanding the processes and the design of the control system. Readers interested in a detailed review on multiscale modeling and control related aspects are referred to [20], [21] and references mentioned therein.

Many chemical and biological systems exhibit phenomena that span ten or more orders of magnitude in time and length scales, ranging from atoms, ions, and molecules to macroscopic, see Fig. 3. Particular simulation methods are most effective at certain scales, and those that are effective at one scale are often not feasible at other scales.

For example, the stochastic dynamics associated with molecular length scales in a small spatial domain are often and most effectively modeled as molecules moving between discrete spatial positions, as *continuous-time Markov processes*, using formalisms and algorithms that are described by such terms as *Chemical Master equations* [22], *kinetic Monte Carlo simulation* [23], *continuous-time Markov simulation* [24], and *Gillespie's method* [25]. Trying directly to apply such approaches to larger spatial domains often becomes rapidly intractable. The number of molecules in macroscopic systems and the number of possible chemical interactions between these molecules for most manufacturing-scale systems are too large for the continuous-time Markov process model to be stored in the memory of a supercomputer, and the computational cost is also too high.

A popular approach for the simulation of such multiscale systems is to employ the most effective simulation model for each set of scales, while dynamically passing information between the simulation models to achieve self-consistency between the scales. Using the example in Fig. 4 for illustration, the dynamics in small spatial domains would be modeled as a continuous-time Markov process and the continuum limit would be applied at the macroscopic length scales so that the model equations can be written as partial differential equations, partial differential-algebraic equations, or integropartial differential-algebraic equations. The sets of dynamic equations at the small spatial domains – the continuous-time Markov processes – communicate with the dynamic equations at the large spatial domains – integropartial differential-algebraic equations – while both sets of dynamic equations are simulated in parallel. These communications need to be designed with care to ensure numerical stability and that the dynamics of the multiscale system are correctly simulated. It has been shown that even very reasonable communication algorithms can lead to very poor results, c.f. [26].

Other examples of multiscale systems are formation of solid-electrolyte interphase during the initial cycles of Li-ion batteries, the nucleation and growth of protein, pharmaceutical and amino acid crystals in microfluidic devices, c.f. [27], [20], [28], [29].

A. Coupling multiscale simulations: a control perspective

The coupling of different simulation strategies for multiscale systems provides many challenges. Dynamically, the coupled simulations can be represented as structured nonlinear feedback control systems, in which each numerical

method is represented as a discrete-time stochastic or deterministic nonlinear dynamic system. The communication signals are treated as sensing or control signals and the communication algorithms are treated as filters or low-order control systems, c.f. Fig. 5. This view allows the application of robust control theory and nonlinear discrete-time dynamical systems theory for the analysis and design of the communication algorithms, and the use of lifting for handling different integration time steps, compare [30]. The analysis provides a quantifiable tradeoff between computational cost and numerical accuracy, which guides the selection of communication algorithms based on the available computation. The resulting simulation code, structured in form of a control loop for the electrodeposition of copper within a trench to form a copper interconnect in a microelectronic device is shown in Fig. 6. Such simulation codes can then form the basis for the controller design, e.g. based on optimal control methods [20].

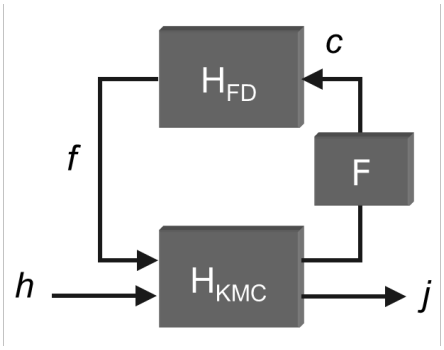

Fig. 5. Block diagram for two coupled simulation codes with a filter introduced to the communication path from one simulation code to another [30].

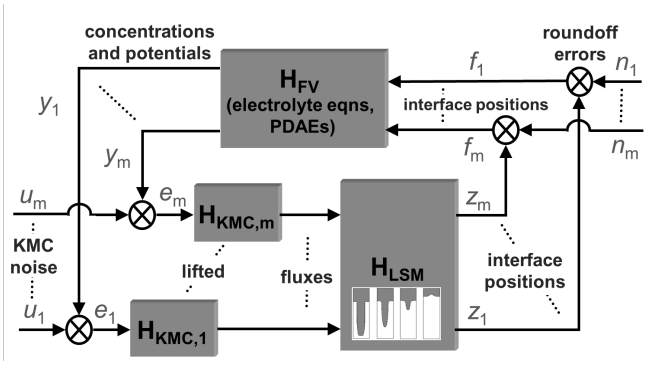

Fig. 6. Block diagram for the coupling simulation codes in Fig. 2 [26]. For example roundoff errors can be compensated by suitable feedback loops for numerical stabilization.

B. Outlook and challenges

The field of structured and control-oriented coupling of simulations on multiple scales is still in its early stages. There are many challenges which need to be tackled. For example, the exploitation of sparsity of theory and algorithms for the design of numerically stable and accurately dynamically coupled multiscale simulation codes is still widely open. Such methods are the base for model-based control of multiscale systems, as for example the control of self assembly and molecular manipulation of large molecules, c.f. Section IV.

III. Control of probe based imaging on a molecular scale

Imaging technologies that provide molecular resolution such as atomic force microscopes (AFM) and scanning tunneling microscopes (STM) have seen significant advancements with respect to speed and image precision over the last decades. While there are many drivers for these advancements, one of the main reasons are tighter and more advanced control approaches. For a detailed review we refer to [11], [10], [31], [9], [13].

We focus on two topics, the integrated design – including the control loop – of AFMs exploiting miniaturized microelectromechanical system (MEMS), and the application of controlled thermal noise to identify material properties.

A. Integrated design and control of atomic force microscopes

The atomic force microscopes are crucial instruments for studying and interrogating material surfaces on the subnanometer scale. AFMs belong to the scanning probe microscopes, c.f. Fig. 1. An AFM produces 3D topographical images of a sample by probing its surface with a sharp tip attached to the free end of a microcantilever, see Fig. 7. The sample is raster-scanned over a surface area. Interaction forces between the tip and the sample cause the microcantilever to deflect. The deflection measured at each scan point, which is a representation of the sample height, can then be plotted as a function of the tip's lateral position to generate the 3-D image of the surface. The versatility of AFMs and their unique abilities to investigate sample surfaces in air, vacuum and liquid environments have led to the development of a large number of operating modes, e.g. contact, semi-contact and non-contact modes are widely

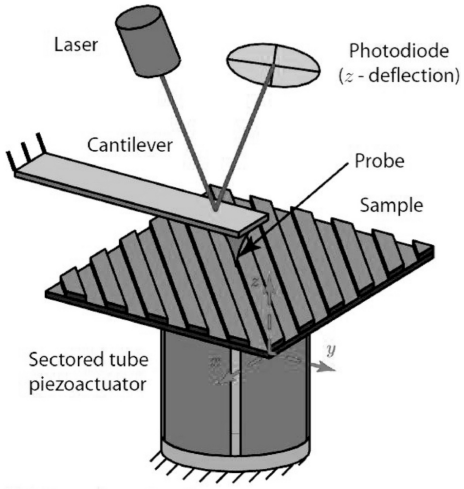

Fig. 7. Components of a typical atomic force microscope.

used [32], [31]. These developments have paved the way for substantial advancement in a variety of fields since the invention of the AFM in the 1980s [33], including in biological and life sciences [34], [35], [36], semiconductor metrology and manufacturing [37], [38], [39], nanofabrication [40], [41], [42], and high-density data storage systems [43], [44], to name a few. The AFM's ultra-sharp tip, a few nanometers wide, enables it to achieve a magnification orders of magnitude better than conventional optical microscopes [3].

Despite these advantages, the cost and size of commercial AFMs makes them accessible only to large laboratories and highly specialized disciplines. If the purchase cost of the AFM, as well as its weight and size, are significantly reduced, the technology can be made available even to schools, small firms and laboratories and it will pave the way for its use in a myriad of applications. A contributor to the size and weight of the AFM are its electromechanical components. In particular, the scanner is either a dense solid piezoeletric tube, or a flexure-guided nanopositioner machined out of a solid piece of metal, which is then actuated using two or three dense piezoelectric stack actuators. Recently it has been shown that the replacement of the AFM nanopositioner with a MEMS device allows for a decrease in cost and widespread usability [45]. This, however, requires a tight integrated design of the control and the mechatronic system. Fig. 8 shows different realizations of AFM systems using MEMS technology and standard piezo technology. A scanning elec-

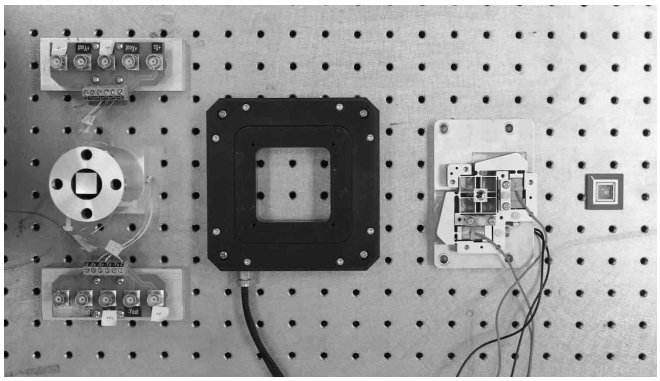

Fig. 8. From left to right: a piezoelectric tube scanner; a 2D flexure-guided nanopositioner; a 3D flexure-guided scanner; and a MEMS nanopositioner. The MEMS device has a scan range and a bandwidth comparable to the rest of the devices shown here [45].

tron micrograph of the MEMS nanopositioner is shown in Fig. 9. The device has a $3\,\text{mm} \times 3\,\text{mm}$ scan table located at the center, and clamped beams that are used as mechanical suspension. U-shaped shuttles are implemented on each side of the stage that provide a base for the actuating electrostatic combs. The generated force from the electrostatic actuators is transferred to the scan table by the U-shaped shuttle and flexures. The design minimizes in-plane rotation, resulting in significant cross coupling reduction. It has a resonance frequency of just under 1.3 kHz, making it comparable, if not better than many commercial AFM scanners. The differential actuation mechanism allows it to operate in the linear regime with a scan range of 20 μm.

Rastering is widely used in AFM commercial scanners, and is a bottleneck in achieving high scan speeds. The raster pattern contains sharp corners that require the scanner to track very high frequencies. In order to avoid exciting the resonant dynamics of the scanner, the scan frequency is typically limited to about one percent of the scanner resonance frequency, i.e. 13 Hz in case of the scanner shown in Fig. 9. To achieve higher scan speeds, smooth non-raster scan patterns in AFM [47], [48], [49] have been proposed. In particular, Lissajous pattern can be generated by tracking sinusoidal signals with well defined frequencies in x and y axes of the scanner, c.f. Fig. 10.

The control system designed to implement this type of scanning in MEMS based nanopositioner is shown in Fig. 11. The controller contains two feedback loops. The inner loop compensator is a damping controller which augments damping of the resonant mode of the nanopositioner. The controller identified as IMC1 is an internal model based controller. In particular, $C_1(s)$ is designed to guarantee steady state tracking of the sinusoidal set-point with frequency ω_x. Due to tolerances associated with MEMS fabrication, there is a small amount of nonlinearity in the dynamics of the nanopositioner that generates harmonics and leads to unacceptable positioning error. In particular, the $2\omega_x$ harmonic was identified as a key contributor to this error, and $C_2(s)$ controller was incorporated to reject this harmonic. The control system allows us to scan as fast as 410 Hz, which is significantly better than what is achievable in open loop and with a raster-based scanning, i.e. 13 Hz.

The MEMS scanner is very suitable for atomic force microscopy. Batch processing makes it inexpensive and its drive and sensing electronics are significantly less complex, and hence more economical than its macroscale competitors. However, due to its size, it is only suitable for scans that involve small samples, e.g. micro or nanoparticles, cells, strands of DNA, etc. Current efforts aim to incorporate all electromechanical components of the AFM in a single MEMS device. That is, to design a MEMS chip that contains a nanopositioner, displacement sensors and a microcantilever with self-sensing capability. Such a device can replace a macro-sized atomic force microscope at a fraction of its cost, bringing the technology within the reach of schools, small firms and other groups that typically cannot afford such a technology. A first prototype is recently reported in [50], with more substantial results to follow.

B. Exploiting controlled noise to identify properties of matter

In SPM, especially AFM control is often used to reject noise, e.g. from vibrations or thermal noise. However, controlled thermal noise can also provide to identifying properties of matter at the nanoscale, c.f. [51]. Fig. 12 shows a control loop, in which a micrometer dimensional flexure probe is used to interrogate matter where the shifts in the effective resonant frequency of the cantilever probe determined by analyzing its response to thermal noise is

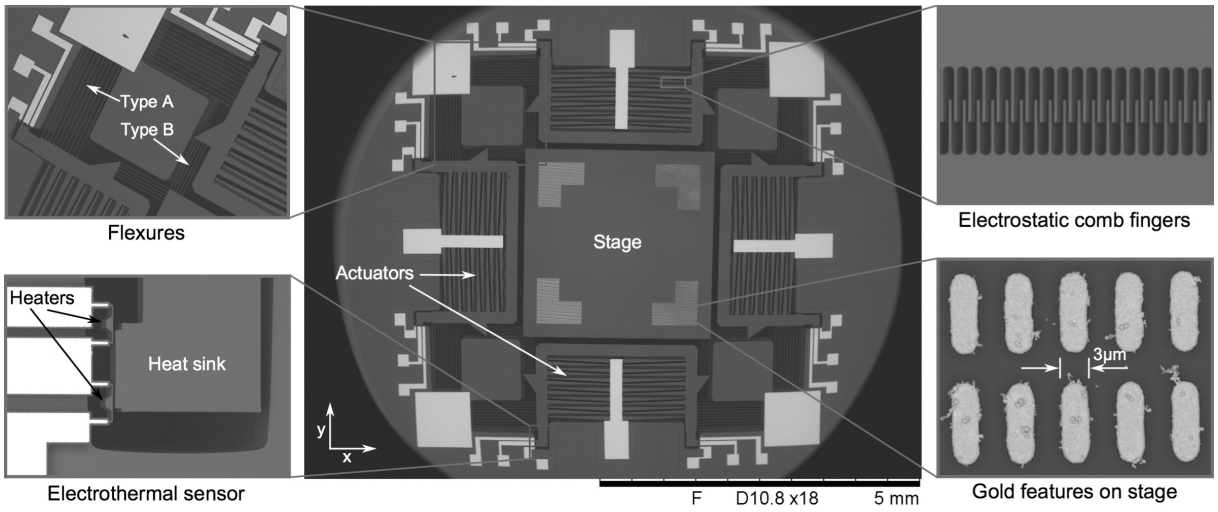

Fig. 9. Scanning electron microscope images of the fabricated nanopositioner, with close-up views of the electrostatic actuators, gold features, electrothermal sensors, and flexures [46].

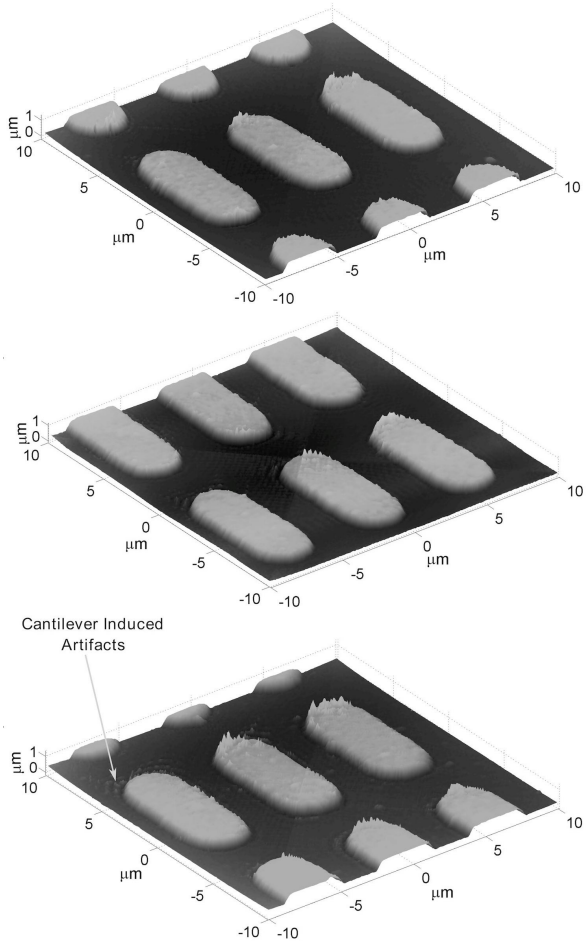

Fig. 10. AFM images generated using the Lissajous non-raster scan method. Starting from the top 210 Hz, 310 Hz and 410 Hz scan rates.

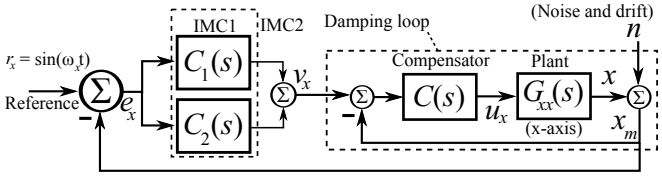

Fig. 11. Block diagram of the x-axis control loop of the MEMS based AFM.

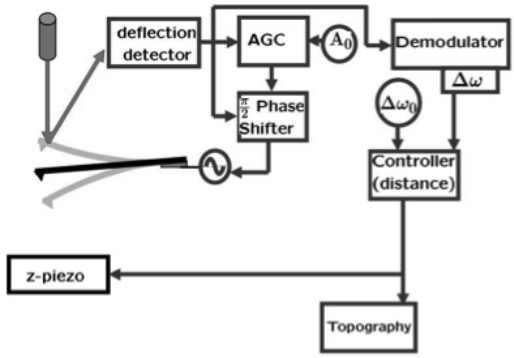

Fig. 12. Cantilever with a sharp tip is excited sinusoidally. The cantilever is excited at its effective resonant frequency, which is governed by the sample that sits on the z-piezo.

used to quantify properties of the sample. Fig. 13 shows the response of the controlled loop, which allows to discern oscillations of very small amplitudes. The underlying principles are specialized where multi-tone frequency based excitation improves signal to noise ratio, which can be used to map elastic and dissipative properties of polymers (see [52]).

C. Outlook and challenges

We outlined two specific fields of control used in probe based imaging, specifically AFM, on a microscopic scale. While control allowed to increase speed and precision, there

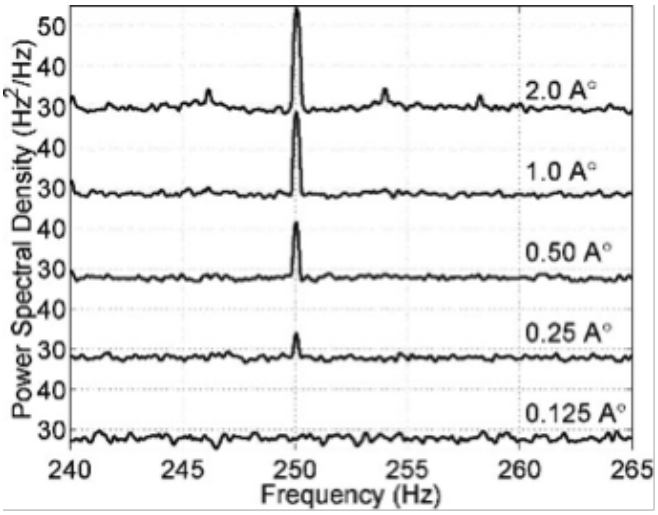

Fig. 13. Control methods used to discern persistent oscillations of the sample-with amplitudes as small as 0.25 Angstrom.

are many open issues [13], [10], [11]. For example, piezoelectric actuators degrade over time and possess properties such as hysteresis and creep effects. Is it possible to design control algorithms which can adapt to these changes?

Much more important in the AFM domain is the interpretability of results; AFM is a metrology tool that does not provide error bars. Furthermore, newer modes of investigation of material property other than topography where multiple modes are involved and the cantilever is forced externally with signals that have multi-tones is of importance. As speeds and demand for precision increase, cross coupling between the directions, which are often controlled independently, becomes more and more important. Can one design suitable multi-input multi-output controllers based on simulation models, which span from the atomic level, the mechanical level of the beam and piezo actuators, up to the macroscopic level (c.f. Section II)? Can one design control and analysis methods that allow investigation of material properties by exciting multiple modes of the probe? Furthermore, methods for uncertainty quantification of the measurements, such as error bars, are needed.

IV. Controlled self organization, manipulation and transport on a molecular level

There are two basic approaches to controlling materials at small length scales. One approach is direct manipulation, single molecules or groups of molecules are individually placed – manipulated – into the desired position. Although simple in concept, this placement is non-trivial at the micrometer and nanometer scales. Technologies including optical tweezers and atomic probes can provide this sort of actuator authority [18], [9], [53]. While molecular manipulation provides means to position and move single molecules, the placement of atoms one-by-one is in general tedious and slow [53], [9]. To overcome this challenge, arrays of probes can be used to provide some level of scale-up, but there is still a large gap up to the macroscopic scale.

The other approach, controlling materials by self-assembly, can provide means to mass produce large quantities of molecules of desired properties and structure. In self-assembly, a collection of atoms or molecules is allowed to arrange on its own, according to its natural dynamics [16]. These dynamics are governed by interactions among the molecules as well as interactions between the molecules and an externally applied field. Control can then be applied to self-assembly by manipulating the strength, or other characteristics, of the field [17], [54]. In general, the dynamics of all molecules are affected when the field is changed, but they are not always affected in the same way, depending on their position and conformation.

Besides manipulation, either by controlled self-assembly or molecular manipulation, the transport on a molecular level is a key step for a success of molecular production. In this section we consider all three problems. Section IV-A focuses on the control of self-assembly, while in Section IV-C the control aspects and challenges of molecular manipulation are outlined. Section IV-B contains a description of the control mechanisms present in molecular transportation.

A. Control of self-assembly

All fabricated materials are assembled from atoms or molecules, but the assembly process is not always explicitly modeled or controlled. Dynamic inputs are used to influence material properties; for example, in traditional processes such as annealing of metals by slowly ramping down the temperature, and in recent methods for colloidal assembly that employ periodic switching of an externally applied magnetic field [55]. The manufacture of flexible electronics from polymers is one example where molecular assembly cannot be ignored. Flexible electronics could provide new products and markets for wearable and disposal electronics, if roll-to-roll manufacturing can be developed [56]. However, during processing, the polymers assemble into microscale fibers that strongly influence the electronic mobility of the materials, and therefore the device performance. The relationship between process, material structure, and material properties is currently not well-understood or quantified, and this limits advances in molecular design and process optimization. Flow, temperature, and ultraviolet light exposure were recently used to improve carrier mobility in poly hexylthiophene polymers, although the underlying mechanisms are not yet fully understood [57]. Fig. 14 illustrates the process, characterization data, and a proposed assembly mechanism. When real-time measurements of the process are available, it is also possible to apply feedback control to direct a self-assembly process. Feedback was applied to a colloidal assembly process [58], in which hundreds of microscale particles are arranged into a crystalline configuration by manipulating the strength of an applied electric field. Model-based optimal control of a similar process was proposed and demonstrated using dynamic programming [59], with the experimental implementation currently under review.

The overall approach to controlling self-assembly is shown

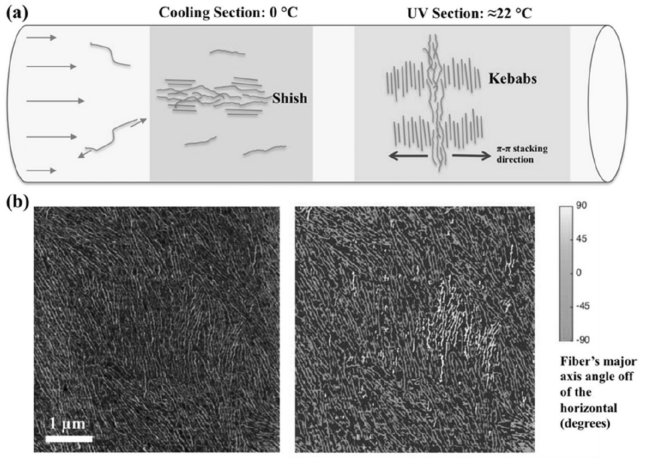

Fig. 14. (a) Proposed mechanisms of nucleation and growth in the flow-cooling-UV system. In the cooling section, solution instability and shear force causes the formation of shish nuclei. The stacks align with the flow as they grow longer in the UV section. (b) Left: AFM image of the surface of the device. Right: same image, segmented for the identification of nanofibers and their angles off of the horizontal. (a+b) Adapted from [57].

in Figure 15. First, the dynamics of the system are sampled and used to identify a reduced-order state that describes the relative positions and overall arrangement of the particles [60]. Then, the reduced-order state and the input space are discretized, enabling the construction of a Markov state model. The transition probability from each discrete state to another is estimated using sampled data. The data already collected may be used for this purpose, and new data may also be collected at that point in order to observe the transitions from each state under each input setting. With the Markov state model at hand, it is then possible to compute the optimal feedback policy using the Markov decision process framework [61], a form of dynamic programming. This approach was used in [59] to achieve a highly crystalline state. A similar approach to feedback control was taken in a molecular crystallization process [62]. In this case, full state feedback of each molecule's position was not available. However, this is not actually necessary, as long as the reduced state can be measured or estimated. In this crystallization process, real-time process sensors were used to infer the total mass of solid crystallized material, using an infrared measurement for the solution concentration, as well as the known initial mass in the system. A second process sensor, the focused beam reflectance measurement, quantifies the backscattered light from the crystal population. Although this measurement quantifies the length of each chord passed by the laser, here only the total number of counts was used, as a surrogate for the number of crystals. Having the mass of crystals as well as the number, the average crystal size can be inferred and therefore controlled [63].

The control that was applied in [63] was rule-based, Ref. [62] shows how the process sensors can be used to construct an empirical dynamic model, which is then used by dynamic programming to compute the optimal feedback policy. The method was tested in simulation and then in experiment, and provides a pathway to reach target properties within a fixed batch time. The study shows that full state feedback is not required, as long as the measured quantities are sufficient to distinguish between configuration types and to define a complete dynamic state.

B. Control and robustness of transportation by microtubes

Transportation, as well as the separation of molecules in a guided and controlled way are, besides the formation and generation, elementary steps for molecular production systems. While probe based molecular manipulation, as described in Section IV-C provides one mean to transport molecules, it is not of use for large amounts of molecules to be transported. One way to achieve molecular transportation might be to copy microtubules inside cells, see Fig.16 and [64]. Inside cells, molecular motors carry cargo from sources to destinations on tracks formed by microtubules. Microtubules are directed lattices with a plus and a minus end. Kinesins carry cargo to the plus end whereas dynein carry cargo to the minus end. The stalk of the kinesin molecule is close to 100 nm and it walks with 8 nm steps. Thermal noise leads to random motion with root mean square value in the 8nm range. Microtubules are formed by dimers which create an asymmetric electrical potential to enable Brownian ratchet mechanisms. Of particular importance is that this transport system on a nanoscale – a molecular machine par excellence – achieves remarkable robustness under a highly uncertain environment, see [64], [65]. The primary means of investigating forces exerted by motor proteins and how they respond to forces is realized by trapping the cargo carried by these proteins in optical force fields. Forces in the femtonewton range are typical at the molecular scale which can be easily studied using optical traps. Traps in the linear Hookean approximation offer stiffness coefficients low enough such that the deflections caused by femtonewton forces are measurable. The primary challenge here is to regulate the desired forces on the motor protein while deciphering the steps taken from noisy behavior of the cargo carried by the motor protein (see [64], [65]).

C. Controlled molecular manipulation

Like in [7], one perspective of our contribution is the control of matter at the atomic scale, the ability to build molecular devices (e.g. electrical circuits) and machines. Besides synthesis of the molecules – the building blocks – this requires the ability to manipulate single atoms, as well as large molecules with atomic precision in a controlled and robust way, c.f. Fig. 2 (left). There exist multiple ways to achieve this task, from SPM-based approaches [9], to optical and magnetic tweezers.

The controlled manipulation becomes especially challenging in the case of complex molecules due to the, compared to the manipulation of single atoms, many degrees of freedom, c.f. Fig. 17. It becomes even more challenging in varying environments, e.g. if the surface structure a molecule should be placed in is highly variable.

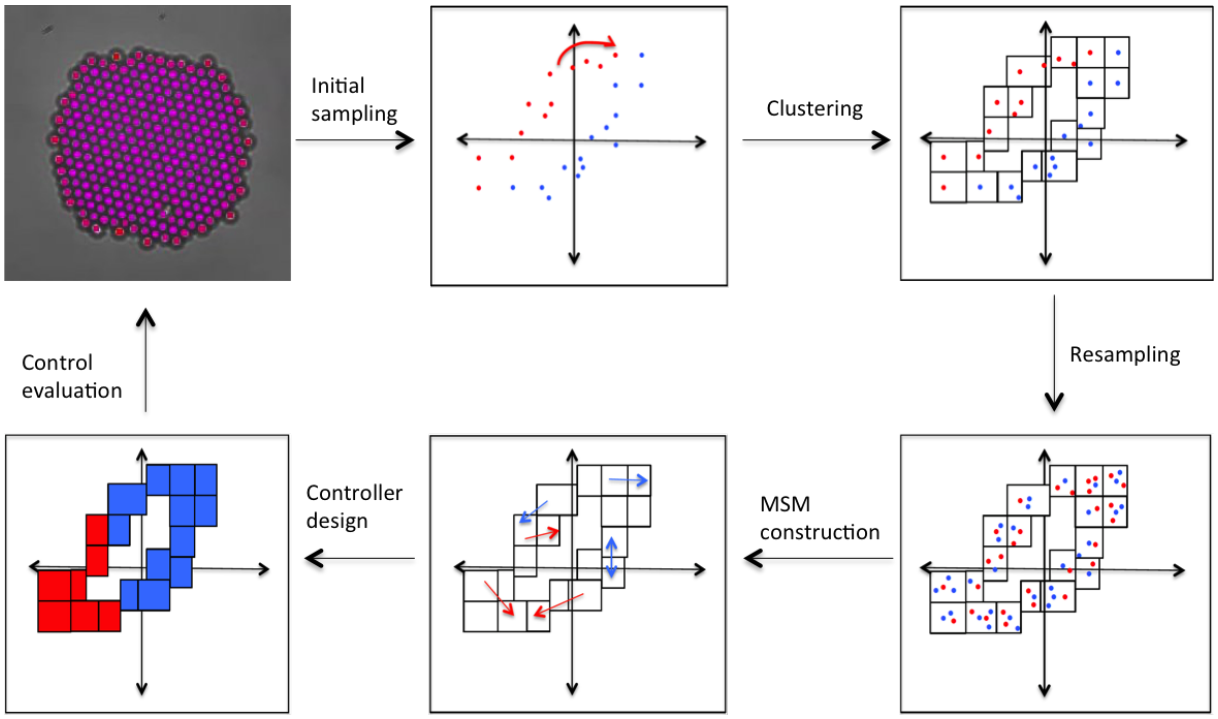

Fig. 15. One approach to modeling and control in self-assembly.

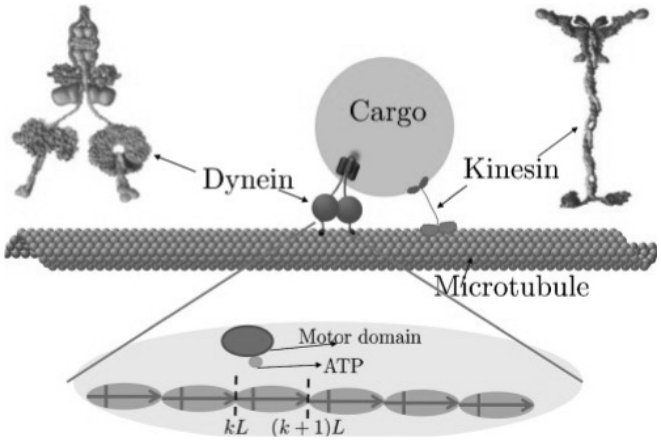

Fig. 16. Microtubes for transportation insides cells

In this section we discuss the appearing questions related to the task of automatically precise, controlled manipulation. In comparison to most existing works, c.f. [9], [11], we focus on the manipulation of complex molecules, consisting of multiple atoms.

a) Scanning probe microscopes for molecular manipulation: In a development that dates back to 1990, SPMs have been used for the controlled manipulation of atomic scale objects on surfaces (typically lateral displacement of adsorbed atoms or molecules) by "dragging" with the tip [18]. The first result of that kind was the famous IBM logo written with 35 Xe atoms. Typically this kind of manipulation has two prerequisites that complicate the used SPM instrument. These are (1) ultra-high vacuum required for the preparation of clean sample surfaces, and (2) cryogenic temperatures (typically liquid Helium = 4.2 K) to freeze out thermal motion (diffusion) of the species to be manipulated over the surface. Atomic and molecular manipulation in such experimental setups is the current state of the art with many examples available in literature [66], [67]. However, in practically all these experiments the molecules are manipulated as if they were point objects without internal degrees of freedom. In this case (as well as for atoms) there is a perfect match between the two lateral degrees of freedom of the molecule and of the tip.

Of much more practical, as well as control interest, is the manipulation taking explicitly the atomic coordinates of the molecule (and of the surface) into account. This adds a large amount of complications since it creates a strong imbalance between the degrees of freedom of the molecule, such as rotation, bending of single bonds, and of the tip - the actuator.

Many questions arise: How can one contact an individual molecule with the SPM tip? How to move the SPM tip to bring the molecule from an initial to a desired final configuration (position, orientation and distortion)? How can we estimate the configuration of the molecule during this manipulation and how can we confirm that the estimate is correct, since typically the actuator is also the only available sensor.

All of these questions provide control challenges, which we sketch in the following.

b) Molecular manipulation by frequency-modulated non-contact atomic force microscopes: One of the biggest problems for molecular manipulation is the fact that the

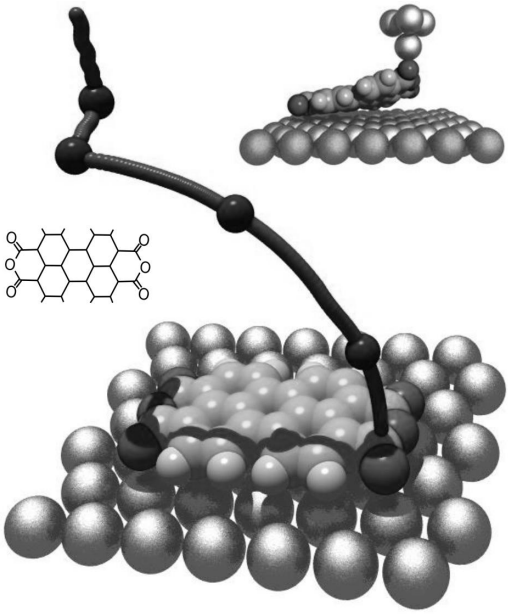

Fig. 17. Single molecule manipulation: PTCDA molecule contacted and lifted by the tip (top right) and molecule lying on the sample surface together with a possible lifting trajectory [19]. The molecule's structure is displayed on the left.

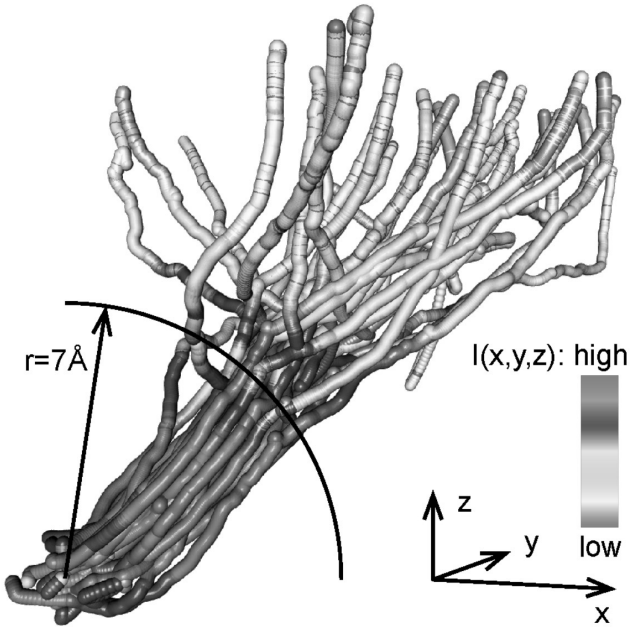

Fig. 19. Successful lifting trajectories. The grey levels indicates the measured vertical force gradient. Picture taken from [53].

measurement capability of the SPM is strongly limited during a manipulation. Hence, true feedback control is usually infeasible. One way to, nevertheless, maximize the amount of available information during manipulation is the use of a frequency-modulated non-contact atomic force microscope (FM-NC-AFM) (c.f. Fig. 18) using, for instance, a qPlus-Sensor [68]. A qPlus-Sensor consists of a quartz tuning fork

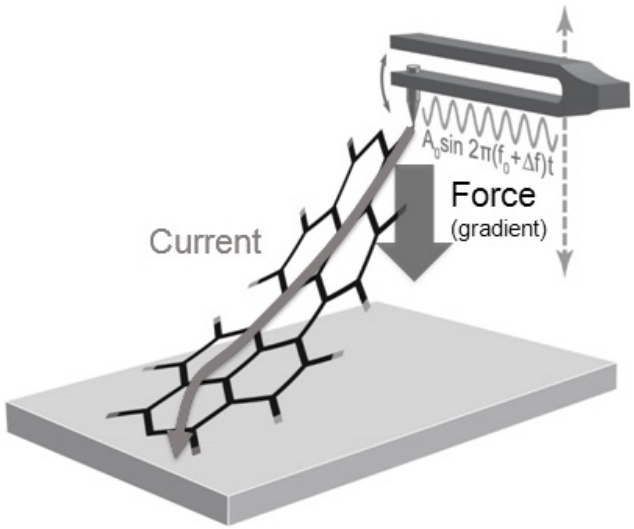

Fig. 18. Frequency modulated non-contact AFM.

with a high spring constant, which has a metal tip glued to the end of one prong. The AFM is self-sensing since the oscillation of the mechanically excited fork creates a detectable piezoelectric current. This principle allows (resonant) oscillation amplitudes as low as 0.02 nm which is important for molecular manipulation. Any force gradient acting on the tip (in the direction of oscillation) changes the effective spring constant of the sensor and thus its resonance frequency. Detecting this frequency shift Δf, one can thus measure the gradient of the tip-sample force (which could be caused e.g. by a molecule suspended between both). This simultaneous measurement of the force gradient during manipulation provides the necessary condition to make true feedback control for molecular manipulation feasible. Furthermore, as we show later, it opens up possibilities for the generation of manipulation trajectories.

The qPlus-Sensor also allows to measure the current through the surface-molecule-tip-junction. This is an additional online measurement that can possibly be used for feedback control.

The general manipulation of molecules implies actions such as lifting, moving and dropping. The goal is to perform these tasks automatically, despite of the manifold challenges the setup presents:

Molecule neighborhood: The surroundings of the manipulated molecule has drastic effects on the manipulation task, in particular the interactions with the surface, on which the molecule is adsorbed, and with other nearby adsorbed molecules. *Uncertain physical phenomena:* Phenomena that are present at the considered scale and are still not completely understood qualitatively and quantitatively, the latter resulting in possible model uncertainties and uncertainties in the control algorithms. *Nonlinearities:* The forces acting in the sample-molecule-tip junction are highly nonlinear. *Limited availability of measurements - no observability:* The inherent problem of SPM techniques is that one can either image

or manipulate but not both at the same time. *Unknown tip properties:* The quality of the tip has a big influence on the manipulation, especially on the strength of the tip-molecule-bond. Unfortunately, the exact tip properties are usually unknown. Hence, this circumstance introduces more uncertainty into the system [69]. *Discontinuities:* Molecular experiments are usually conducted on a corrugated surface [70]. This corrugation modulates the molecule-surface force and leads during manipulation (e.g. lifting) to instantaneous relaxations of the molecule into different configurations/positions (see Fig. 21). Such relaxations break the reversibility of the manipulation process.

We focus in the following solely on the task of lifting a molecule. For isolated molecules this can be a rather straightforward task; for molecules adsorbed within an island of other molecules it is not so easy anymore. In [53] it could be shown that a specific molecule can indeed be "manually" lifted out of an island of molecules using a human guided lifting procedure. One of the central outcomes is that, due to the intermolecular interaction forces, only very specific trajectories lead to a successful removal (see Fig. 19).

While such a manipulation can be performed manually, this is in general very cumbersome, as it is very time consuming and requires for each molecular environment an initial learning phase to find the feasible trajectories that allow a lift. It is important to note that up to now there are no computationally feasible models that describe the acting forces precisely enough to make accurate predictions of the trajectory while at the same time being fast enough to be used on a routine basis, especially not for varying environments.

Therefore, the employed control methods have to be inherently robust or the uncertainties have to be taken explicitly into account in the controller design. Fig. 20 shows a possible overall control strategy that would allow automatic lifting. It includes a reference trajectory along which the molecule should be moved.

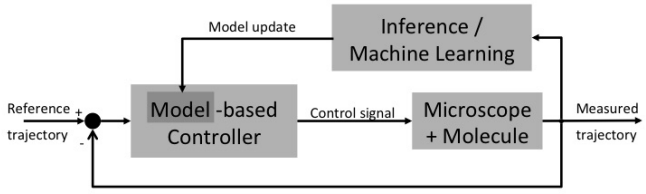

Fig. 20. Possible control strategy for automated lifting of complex molecules.

In order to achieve automatic molecular manipulation, the reference trajectory has to be generated automatically. This can be accomplished using a physical simulation that models the interaction forces between surface, molecule, nearby molecules and the microscope tip. One specific modeling approach that is fast enough is the force field (FF) model. We use such a FF simulation, written in C++ and connected to MATLAB, to simulate the molecular manipulation process. Fig. 21 shows the FF simulation, where a molecule is contacted by the tip, which performs a vertical lift and the resulting trajectory of the center of gravity (CoG) of the molecule is computed. It can be seen that, although the tip is lifted in equidistant steps, the molecule relaxes, due to the corrugated surface, instantaneously and nonreversibly into different configurations (indicated by the large steps in the CoG trajectory).

This simple simulation experiment shows that the FF model contains the necessary ingredients to compute manipulation trajectories, which can then be tested on the actual microscope.

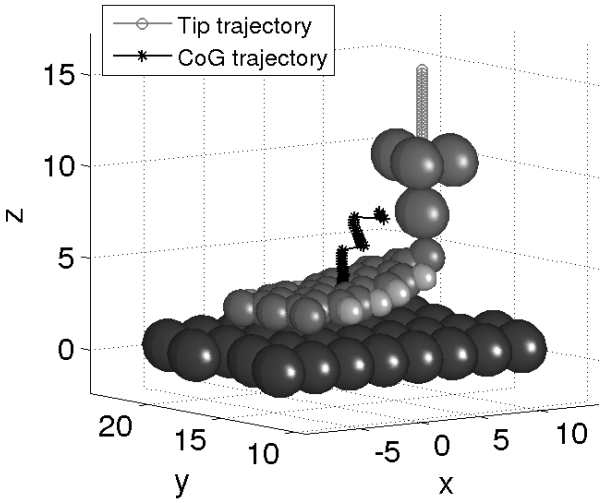

Fig. 21. 3D Force field simulation: The figure shows a PTCDA molecule, consisting of 38 atoms, lying on a substrate made out of gold atoms. The molecule is shown in its initial configuration lying on the surface and being contacted by the tip (illustrated by its last four atoms right above the molecule). The tip is lifted vertically pulling the molecule with it. The resulting molecule movement is represented by the trajectory of its center of gravity (CoG). The axes' units are Angstroms.

Once a trajectory is found, algorithms from machine or iterative learning can be used to update this optimal trajectory, which can then be used for the design of new optimal trajectories for the lifting of nearby molecules. In order to maximize the probability of a successful lift, path following control can be employed to compensate for disturbances and model uncertainties.

c) Application of molecular manipulation - scanning quantum dot microscopy: A recently developed application that originated from molecule manipulation is Scanning Quantum Dot Microscopy (SQDM) [71]. It requires a specific molecule, acting as a quantum dot, hanging from the tip of a FM-NC-AFM, c.f. Fig. 22. Hence, the successful lift of a molecule is a necessary prerequisite to this microscopy technique. SQDM is a highly sensitive method to measure electric potentials on the atomic scale: The sample to be analyzed is discretized in pixels and the tip (with the quantum dot) is moved from pixel to pixel. At each pixel, the bias voltage between tip and sample is varied within a specific interval and the force gradient response is measured. This response is called the *spectrum*. After going through all pixels, the spectra and their specific properties are then

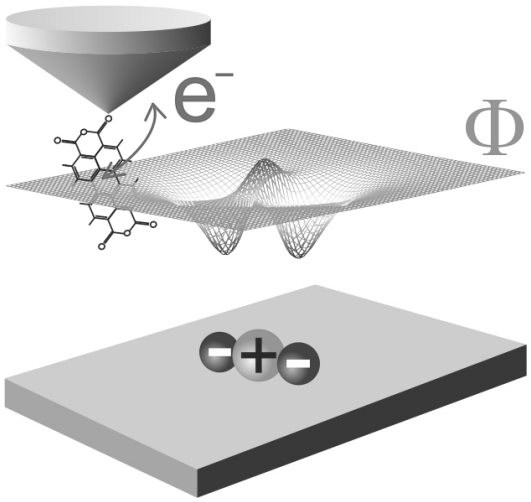

Fig. 22. Illustration of the SQDM measuring principle: depending on the local electric potential field of a nanostructure on the surface of a sample, a single electron jumps from the tip of the microscope to the sensor molecule or back.

compared against each other, yielding an accurate picture of the electric potential at the measured height (for more details see [71]).

Currently, this is done in a non-optimized way (mainly due to limitations in the current measurement instrumentation and method of acquiring and processing data). Combining extremum tracking control approaches and the use of *a priori* knowledge of the characteristic SQDM signal promises improvements in the scanning speed in the order of one magnitude. Additionally one can exploit well investigated methods of AFM x-y-z control, see Section III with the SQDM objectives, e.g. imaging equipotential lines of the electric potential field at a specific height.

V. Conclusion

There are growing opportunities for control of nanoscale and molecular systems, which are driven by technological advances in sensing, actuation, and computation. The key aspects of this field can be understood through distinctions such as self assembly and molecular manipulation, probe based imaging and through specific case studies and experimental implementation at a range of maturity spanning from commercially available products up to research level devices. Besides application oriented challenges, control of molecular systems also provides a series of fundamental control questions. Is it possible to exploit sparsity together with control theory in the design of numerically stable and accurate dynamically coupled multiscale simulation codes? What is a suitable, sparsity exploiting control theory and what are suitable algorithms for analyzing and designing controllers for systems with high-dimensional stochastic nonlinear dynamics? Is it possible to design closed-loop controllers that can adapt robustly to changing parameters? What are suitable strategies to control and at the same time manipulate molecules with the probe being the actuator and sensor? How can one design controllers that are based on a fusion of first principle models with uncertain model components? Which control approaches can handle global and local (fast and slow) dynamics at the same time? What are suitable model reduction techniques for the appearing large scale models?

Summarizing, we believe that control on a molecular level is a very rewarding research field, offering a variety of opportunities far beyond the pure application of existing approaches.

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