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The principle and improvement scheme of single-molecule magnetic tweezer manipulation technology

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ABSTRACT
In the single-molecule manipulation technology, magnetic tweezers technology has infinite potential, this paper mainly introduces the principles of optical tweezers, scanning probe microscopy (SPM), and magnetic tweezers, and focuses on the application of magnetic tweezers technology in recent years, and proposes an improvement scheme of magnetic tweezers system.

KEYWORDS
magnetic tweezers; single molecule manipulation; multipole magnetic tweezers system; TEM image

1 Introduction

Nowadays, medical care is the foundation of people's healthy life, and bioscience and technology are the cornerstone of medical level. In order to study the monomolecular structure more deeply and cure more diseases, researchers use electronic control systems to manually control microgrippers and glass microneedles to realize the operation platform for multiple operations on target cells [1-2]. However, this technique currently relies on robotic-assisted minimally invasive surgery (MIS) technology, which improves the precision and flexibility of the instrument[3]. However, MIS technology remains largely absent in surgical applications within constricted, confined workspaces (e.g., neuroendoscopy), with the limitation of the lack of small, dexterous robotic tools. Recently, many research works have focused on optical tweezers, glass microneedles, magnetic tweezers, Stokes dragging, etc., among which magnetic tweezers are relatively rare; In contrast, magnetic tweezers have the advantages of a large force range, non-contact operation, and high spatial resolution, which can provide spatial resolution of up to 5-10 nanometers, and can be measured on millisecond time scales [4-5]. This paper focuses on the basic principles and applications of magnetic tweezers, and provides ideas for improving magnetic tweezers.

2 Principle

Single-molecule manipulation technology is a category of single-molecule scientific research, and it is an emerging marginal discipline. It refers to the precise control and operation of a single molecule through physical, chemical or biological means to directly observe and study the structure, kinetic behavior and intermolecular interaction of a single molecule, so as to reveal the physical, chemical and biological properties at the molecular level. At present, the single-molecule manipulation technology that has been developed focuses on optical tweezers, magnetic tweezers, scanning probe microscopy, etc. [6].

2.1 Optical tweezers

Optical tweezers are a technology that uses laser beams to manipulate tiny objects, and their basic principles are mainly based on the momentum transfer and gradient force effects of light. Gradient Force is used to achieve stable capture of particles. The gradient force is generated by the spatial variation of the laser beam intensity; At the center of the laser beam, the light intensity is the highest, while at the edges, the light intensity is lower. The particles are attracted to the most intense light, at the focal point of the beam. The direction of this force coincides with the beam intensity gradient and hence the name gradient force. Numerical aperture (NA) objectives, on the other hand, focus the laser beam into a high-density field region, forming an optical trap or "optical tweezers" [7]. In this region, the particles are stably fixed at the focal point by a combination of radiative pressure and gradient forces.

2.2 Scanning Probe Microscope (SPM)

SPM consists of techniques such as STM (Scanning Tunneling Microscopy) and AFM, which enable the observation and manipulation of individual molecules at atomic resolution. STM is based on the quantum tunneling effect, which means

that when the distance between the tip of the needle and the sample is very small (usually less than 1 nanometer), electrons can pass from the tip of the needle through the barrier to the surface of the sample through the quantum tunneling effect, forming an electric current. This current is exponentially related to the distance between the tip and the sample, so the distance between the tip and the sample can be precisely controlled by measuring the tunneling current, enabling a scan of the surface topography of the sample. The AFM, on the other hand, uses a nanoscale probe mounted on an elastic cantilever fixed at the other end. When the scanner moves, the force is inconsistent due to the undulation of the sample surface, resulting in a slight shape or amplitude change in the cantilever that is the physical quantity detected by the AFM system. In general, STM and AFM complement each other, with STM being suitable for conductive samples and AFM compensating for the limitation that STM cannot directly image non-conductive samples.

2.3 Magnetic tweezers

The magnetic tweezers system is usually composed of a magnetic circuit system, a microscopic imaging system, a data acquisition and processing system, a temperature control and a room-shaking device.Among them, magnetic beads are a key component in magnetic tweezer technology, and their role is to transfer the magnetic field force to the target molecule. Magnetic beads are typically made of superparamagnetic materials, such as ferrite or nanoparticles, that can be effectively manipulated in magnetic fields. The size, shape, and magnetization of the beads have a direct impact on the performance of magnetic tweezers. For example, larger beads are capable of delivering more force, while smaller beads are better suited for high-precision measurements. In order to manipulate magnetic beads, it is necessary to use the magnetic field gradient to exert force on superparamagnetic microspheres (beads), and by controlling the strength and direction of the magnetic field, it is possible to precisely manipulate biomolecules (such as DNA and proteins) attached to the microspheres. To generate the desired magnetic field gradient, an adjustable magnetic field gradient is typically generated using a permanent magnet (e.g., NdFeB magnet) or by driving a coil with a current. When a superparamagnetic sphere is in a gradient magnetic field, the ball is subjected to a magnetic moment that coincides with the direction of the magnetic field gradient. Specifically, the magnetic force F can be expressed as:F=μ0·μ·∇BF=μ0·μ·∇Bwhere μ0μ0 is the vacuum permeability, μμ is the magnetic moment of the sphere, and ∇B∇B is the magnetic field gradient.The magnitude of the magnetic field gradient determines the strength of the force exerted on the ball. [8] For example, by adjusting the distribution of the magnetic field gradient, it is possible to apply a tensile force or torque to the ball to stretch, twist, or rotate the target molecule.

3 Application

While there are several articles mentioning the basic principles and some applications of magnetic tweezer technology, there are no specific examples or advances in further applications.Nowadays, magnetic tweezer technology is still widely used to study the mechanical properties of biomacromolecules such as DNA and RNA, such as the tensile and folding mechanical analysis of DNA double strands, that is, one end of the biomolecule (usually DNA) is attached to the glass slide, and the other end is connected to a superparamagnetic sphere, plus a magnetic field to attract the magnetic sphere. Changing the external magnetic field allows the paramagnetic sphere to stretch or rotate, thus stretching or twisting the DNA molecule. The ball does a Brownian motion near its equilibrium position, and its position is recorded by an optical microscope. The force on the sphere is calculated according to F = kB T〈L〉/δx2〉, where kB is the Boltzmann constant, T is the temperature, 〈L〉 is the mean end distance of the DNA, and δx is the offset of the ball relative to its equilibrium position. and the study of the mechanical properties of protein-nucleic acid interactions. In addition, this technique has been used to study the dynamic structure and function of chromatin, as well as the mechanical behavior during protein folding. In order to achieve long-term stable control of single molecules, some magnetic tweezers technology uses high-precision fixed focus systems and high-speed cameras, and uses advanced microscopic imaging platforms to observe the temporal and spatial distribution of fluorescent molecules, so as to explore the spatiotemporal dynamic evolution mechanism of labeled biological macromolecules. With the advantages of high throughput and high spatiotemporal resolution, it can realize the parallel measurement of nanometer and even sub-nanometer scale spatial information of a large number of fluorescence signals. This is not only used for basic biological research, but also plays an important role in the field of medicine. For example, the stability and unwinding ability of peptidase Rde3 on double-stranded RNA, the role of DNA intercalators in microbial sources, etc.Compared with other single-molecule manipulation techniques, magnetic tweezers are favored because of their ease of construction and high accuracy. Torque can be measured directly with an accuracy of about 1 pN·nm, similar to the ability of optical tweezers to measure force. Recently, a torque clamp configuration has also been introduced, further improving the accuracy of the experiment. However, when the magnetic force is less than 10 pN, the resolution of conventional magnetic tweezers is limited by the Brownian motion of the magnetic sphere. And the requirements for magnetic beads are relatively strict, and the slightest

carelessness will destroy the structure. Magnetic tweezers have a lower spatial resolution, usually in the nanometer range, compared to optical tweezers, which can reach femtometer levels. To improve physical measurements and manipulation within cells, Y. Tsatskis et al. developed a multipolar magnetic tweezer system for micromanipulation that involves submicron position control and picomicroforce control of submicron magnetic beads within a single cell for measurements at different positions (space) and at different time points (time). [9] He uses a general-purpose predictive controller to position the beads in 3D in the cell, which can solve the control challenges caused by the low visual feedback bandwidth of high-resolution confocal imaging. However, the design of a multipolar magnetic tweezer system needs to consider the interaction of multiple forces, including magnetism, drag, gravity, buoyancy, and lift, among others. These forces work together on the multidimensional stage of particle motion, complicating the trajectory of a particle or cell in the field of microfluidics.

4 Improvement measures

From the current situation, it can be seen that the current bottleneck lies in the insufficient spatial control ability of magnetic tweezers for small magnetic beads and the incomplete consideration of the manipulating environment. In order to reduce the influence of the above forces on the magnetic tweezer system and strengthen the control ability of the magnetic tweezers on the small magnetic beads, a complete state space equation of float motion can be established and a state feedback control system with compensator can be designed to solve the coupling problem and decouple the control to improve the response speed and stability of the system [10]. At the same time, in order to reduce latency and improve response speed, digital power amplifiers can be used instead of traditional power amplifiers. [11]This new power amplifier adopts a three-level mode combined with an improved particle swarm optimization algorithm for parameter optimization to reduce current ripple and improve the real-time performance of signal tracking. This solves the problem of low frame rates. In terms of improving the display imaging system, lens electron microscopy (TEM) can be used for image analysis to select the right sample for experimentation, starting with cell lines such as HEK293 cells or PC12 cells, which are commonly used in cellular internalization studies. Fluorescent or colloidal gold markers are used to track the movement of these particles so that the distribution of the markers within the cell can be observed by TEM. Ultrastructural images of cells are taken using high-resolution TEM equipment, which will be used to observe specific details during sample changes; The acquired TEM images are then processed to enhance contrast and clarity for better study of the internal structure of the sample.

Based on the results of the first step of TEM image analysis, a three-dimensional model of the sample change process was established. The model should take into account the distribution, interactions, and internalization pathways of organelles; The Monte Carlo simulation algorithm was used to dynamically simulate the sample change process to predict the changes of sample behavior under different conditions, and the Monte Carlo simulation was used to establish an optical model of the internal structure of the sample, which was verified by experimental data to further optimize the model parameters to improve the prediction accuracy. Furthermore, statistical software was used to analyze the integrated data to verify the accuracy and reliability of the model. Statistical software can choose from Microsoft Excel and GraphPad Prism. These software have been used in several studies to process and analyze data related to cellular internalization, such as viral internalization, exogenous protein expression, endogenous RNA transcription, and transferrin internalization.

5 Conclusion

In recent years, it has been widely used in the fields of biophysics, materials science, nanotechnology and life sciences. However, in terms of molecular manipulation, the results achieved are not as many as STM technology and optical tweezers, and most studies are still in the theoretical research stage.In this paper, the following directions are proposed for the improvement of magnetic tweezers: (1) In order to reduce the influence of the above forces on the magnetic tweezers system and strengthen the control ability of magnetic tweezers on small magnetic beads, a complete state space equation of float motion can be established and a state feedback control system with compensator can be designed. (2) In order to reduce latency and improve response speed, digital power amplifiers can be used to replace traditional power amplifiers. (3) In terms of improving the display imaging system, lens electron microscopy (TEM) can be used for image analysis. (4) The Monte Carlo simulation algorithm was used to dynamically simulate the sample change process to predict the change of sample behavior under different conditions. (5) Statistical software was used to analyze the integrated data to verify the accuracy and reliability of the model. China has vigorously promoted scientific and technological innovation, and incorporated cutting-edge technologies such as magnetic tweezer technology into its national science and technology development strategy. As a single-molecule manipulation tool with high precision and

high response speed, magnetic tweezer technology has been significantly developed in China in recent years. For example, the Institute of Physics of the Chinese Academy of Sciences, the Beijing Research Center for Condensed Matter Physics and other institutions have jointly developed a new type of single-molecule transverse magnetic tweezers based on sheet light illumination, which improves the spatial accuracy and expands the application range. In addition, the School of Physics and Astronomy of Sun Yat-sen University has also made important progress in the fluorescence magnetic tweezers technology laboratory, especially in single-molecule biophysics research.

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