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博 士 学 位 论 文

应用于 DNA 分子电检测的碳纳米管和石墨烯薄膜谐振器件研究

The research on carbon nanotube/graphene film resonator used to electrically detect DNA molecules

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摘 要

脱氧核糖核酸（deoxyribonucleic acid, DNA）是引导生物体生长发育及生命机能运作的重要生物大分子，是大多数生物体的遗传物质。单链 DNA 分子的杂交检测在临床医学上对于疾病诊断、基因检测和环境中生物试剂检测有重要意义。目前，以光学检测、电学检测和电化学检测为主的无标记检测 DNA 分子的方法因为比有标记检测更方便快速而受到广泛研究。其中，电学检测方式简单，成本较低，是当前一种比较普遍的测试方法。碳纳米材料中的碳纳米管（carbon nanotube, CNT）和石墨烯（graphene）表现出极佳的电学、机械性能，是用于制作微型谐振器的绝佳材料。它们独特的原子结构能与生物分子结合，非常适用于生物传感。以此为基础制作的场效应晶体管被用来检测 DNA 的杂交。然而该方法存在测试装置的复杂性，实验无法进行有效重复性的问题。基于此，本文将微型谐振器和生物传感结合起来，探索研究制作碳纳米管和石墨烯微型谐振器并将其用于探测单链 DNA 分子溶液浓度。

传统的微型谐振器件都是硅基样片，其半导体材料属性使得硅器件存在较大的寄生电容，在高频（~MHz）领域会引起较大的损耗，干扰测试精度。本文提出用玻璃基片并结合自对准光刻工艺制造微型谐振器取代传统的硅基样片，之后测试了用玻璃基片制作的器件的寄生电容，作为对比，我们同时测试了同样条件下的硅基片制作的器件的寄生电容。测试结果表明，自对准工艺制作的器件寄生电容为 50fF，而同样工艺制作的硅基器件寄生电容却达到 2 pF。

采用介电泳的方法将碳纳米管有序地组装到器件上，形成两端固定、中间悬空的碳纳米管薄膜。为了验证其电学性能，用半导体参数测试仪测试了器件的类晶体管特性，获得了输出特性曲线和转移特性曲线。接着搭接检测 DNA 浓度的测试系统，利用矢量网络分析仪和前置放大器等仪器测量传输系数 S_{21}，以此来实时检测滴加在器件中的单壁碳纳米管薄膜上的单链 DNA 溶液浓度，并取传输系数 S_{21} 峰值对应的频率为谐振频率。首次与单壁碳纳米管薄膜结合的探针单链 DNA 分子浓度会影响谐振频率，出现所谓的频率红移。随着探针单链 DNA 溶液浓度的增大，谐振频率偏移量逐渐增大。经过探针单链 DNA 分子饱和处理的碳

纳米管薄膜谐振器再次测量与之互补配对的单链 DNA 分子时，显示了与之前相反的现象，谐振频率出现了所谓的蓝移。随着互补配对的单链 DNA 溶液浓度的增大，谐振频率的偏移量也逐渐增大。实时检测时间一般在 60 分钟之内，而且可以获得的 DNA 浓度测试极限为 5 nMol/L。

实际应用中碳纳米管束和碳纳米管薄膜的导电性受其纯度和方向所限，而石墨烯作为二维材料，可在一定程度上弥补了碳纳米管的不足。碳纳米管因其手性角的限制而分为半导体型和金属型，从而影响了碳纳米管自身的电学性能，而目前的分离技术很难获得高纯度的单一类型的碳纳米管。另外，碳纳米管的极好导电性体现在沿着管的方向，而实际上器件中的碳纳米管薄膜很难实现高度的方向一致性。这些都限制了碳纳米管器件的测试性能。石墨烯是由单层碳原子组成的具有蜂窝状的六边形结构，也和碳纳米管一样表现出极强的导电能力和机械性能。

石墨烯在水中的分散性差，易出现团聚现象，而且很难通过介电泳的方式组装在器件上，因此我们用介电泳的方法将氧化石墨烯组装在器件上作为替代方案，形成双端固定、中间悬空的薄膜。在低温（~200℃）的管式炉中，用氢气将器件上的氧化石墨烯薄膜进行原位还原。用扫描电子显微镜和原子力显微镜表征石墨烯的形貌，并用 X 光衍射仪和拉曼光谱仪表征还原前后的氧化石墨烯。此外，测试了还原后的石墨烯薄膜的电学特性，发现在 200℃的条件下，器件上的氧化石墨烯薄膜的还原效果最佳。

用同样的测试系统来检测基于石墨烯薄膜的微型谐振器对 DNA 分子的检测能力。探针单链 DNA 分子与石墨烯表面的结合会让传输系数 S_{21} 与扫描频率的关系曲线出现整体左移，浓度从 5 μMol/L 下降到 5 nMol/L 时，中心峰值对应的谐振频率红移量从 120 kHz 变到 0。而经探针 DNA 分子饱和处理的石墨烯器件测量另一互补配对单链 DNA 分子浓度时，传输系数 S_{21} 与扫描频率的关系曲线则是整体右移。互补单链 DNA 分子浓度为 50 nMol/L 时，中心峰值对应的谐振频率蓝移量为 10 kHz。

最终将碳纳米管薄膜器件和石墨烯薄膜器件的测试结果进行对比，碳纳米管薄膜器件的测试精度较高，但器件重复性较差，而石墨烯薄膜谐振器件则正好相反。这很可能与器件的制备方法和材料的自身性能有关。总的来说，本文探究了一种利用微型薄膜谐振器来实时快速检测单链 DNA 分子浓度的实用方法，这为

以后实现实时原位检测其他生物分子做出一定的贡献。

关键词：微型谐振器；介电泳；单链 DNA 分子检测；双端口网络；热还原

Abstract

Deoxyribonucleic acid (DNA) is an important biological macromolecule to guide the development of biological growth and life function, and it is the genetic material of most organisms.The hybridization detection of single-stranded DNA (ssDNA) molecule shows significance to disease diagnosis, genetic testing in clinical medicine, and it is also important to the detection of biological reagents in the environment. At present, label-free detection of DNA molecules, such as optical detection, electrical detection and electrochemical detection, has been extensively studied becasue it is more convenient and faster than the method based on labeled detection. Among them, the method of electrical detection is simple, low cost, and becomes a common test method. As famous nanomaterials, carbon nanotube (CNT) and graphene show excellent electrical and mechanical properties, are always used to make micro-resonator. Their unique atomic structure can be combined with biomolecules, which indicates that CNT and graphene are very suitable for biosensing. The field-effect transistors produced on this basis are used to detect the hybridization of DNA. However, the testing instruments are complex and the experiment can not be effectivly repeated by using this kind of method. Based on this, the micro-resonator and biosensor are combined to explore the production of carbon nanotubes and graphene micro-resonator. And then the deviced was used to detect the concentration of single-stranded DNA solution.

Traditional micro-resonators are silicon-based devices, and large parasitic capacitance exists between the electrodes of the device because of its own electrical property as semiconductor material. As a result, great signal loss could interference test accuracy when the device is applied high frequency (~MHz). Here we propose to fabricate a micro-resonator with a glass substrate to replace the traditional silicon-based device through self-aligned lithography process. Then the parasitic capacitance of the new device was measured. For comparison, we also test the parasitic capacitance of the device with the same structure based on silicon wafer. The results show that the parasitic capacitance of the micro-resonator fabricated by self-aligned process and based on glass substrate is 50 fF, while the parasitic capacitance of the silicon-based device is 2 pF.

The carbon nanotubes were assembled onto the device by dielectrophoresis in order to form a suspending carbon nanotube film with two fixed ends. To verify its electrical properties, the device was tested with a semiconductor parametric analyzer as a transistor. The output and transfer characteristic curves were obtained. Then we built a test system based on our fabricated micro-resonator, vector network analyzer and preamplifier to detect the concentration of ssDNA. The transmission coefficient S_{21} was recorded after the ssDNA solution dropping on the CNT film of the micro-resonator and the corresponding frequency was seen as resonant frequency when the transmission coefficient S_{21} achieved peak value. The result shows that the resonant frequency is affected by the concentration of probe ssDNA solution when the probe ssDNA molecules bind with suspending CNT film. The resonant frequency decreases, that is, the so-called red-shit occurred. The value of resonant frequency shift increases with the increase of concentration of the probe ssDNA solution. The complementary ssDNA was measured after the micro-resonator with suspending CNT film saturating by probe ssDNA solution, while this time, the result is just opposite. The resonant frequency increases, that is, the so-called blue-shit occurred. The value of resonant frequency shift also increases with the increase of the concentration of complementary ssDNA solution. Real-time detection is finished in 60 minutes and the available testing limit of ssDNA concentration is 5 nMol/L.

However, carbon nanotubes are classified into semiconducting and metal types by their chiral angles, which affect the electrical properties of carbon nanotubes themselves. And it is difficult to obtain one single type of carbon nanotubes with very high purity. In addition, the excellent electrical conductivity of carbon nanotubes is just limited along the tube, and the high degree of directional uniformity is still very difficult to achieve in the real life even though many methods have been proposed. These factors limit the performance of the micro-device based on carbon nanotube. Graphene, a new nanomaterial composed of single layer of carbon atoms with a honeycomb hexagonal structure, also shows high electrical conductivity and good mechanical properties just like carbon nanotube.

Graphene tends to reunion in water because of Van der Waals force between single-layer carbon atoms, so the graphene dispersed in water is not easy to stabilize. Besides, the graphene cannot be easily assembled on the micro-device by dielectrophoresis. Therefore, the alternative plan is to assemble suspending graphene

oxide film by using dielectrophoresis. The suspending graphene oxide film of the micro-resonator was then reduced in situ by hydrogen in a tubular furnace with low temperature (~200 ℃). The morphology of reduced graphene oxide (RGO) was characterized by scanning electron microscopy (SEM) and atomic force microscopy (AFM). Then the electrical properties of RGO film were characterized by X-ray diffractometer and Raman spectroscopy. In addition, the electrical properties of graphene oxide film after reduction were also tested. It shows that the best reduction effect of graphene oxide film on the micro-device occurs at 200 ℃.

The same testing system was used to detect the concentration of ssDNA solution based on suspending graphene film micro-resonator. The combination between probe single-stranded DNA and graphene causes the curve plotted by transmission coefficient S_{21} and the sweeping frequency to appear a whole left-shift. The resonant frequency corresponding to the center peak of the transmission coefficient S_{21} changes from 120 kHz to 0 when the concentration of probe ssDNA decreases from 5 μMol/L to 5 nMol/L. The curve plotted by transmission coefficient S_{21} and the sweeping frequency shows whole right-shift when the micro-resonator was used to measure the complementary ssDNA after saturation treatment with probe ssDNA. The blue-shift of the resonant frequency is 10 kHz when the concentration of complementary ssDNA solution is only 50 nMol/L.

Finally, the test results between the carbon nanotube and graphene thin film devices were compared, it shows that the test accuracy of the carbon nanotube thin film device is higher, but the reproducibility is poor, while it is just opposite for the graphene resonator. This is probably related to the device's preparation method and the material's own performance. In general, we explored a practical method for rapidly detecting the concentration of single stranded DNA by using a micro nano-film resonator in real-time, which will enable real-time detection for other biomolecules in the future.

keywords: micro-resonator; dielectrophoresis; detection of single-stranded DNA; two-port network; thermal reduction

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