A Novel Low Energy Electron Imaging Technique for DNA Sequencing and Surface Analysis

Marian Mankos
Electron Optica, Palo Alto, CA 94301
marian@electronoptica.com

With the continued miniaturization of semiconductors and recording media and emerging opportunities in nanotechnology and biosciences, there exists a growing need for techniques with high spatial resolution, analytical capabilities and surface sensitivity. In genome research, significant demand exists for the development of novel technologies capable of low-cost, high quality DNA sequencing. While established sequencing techniques based on capillary array electrophoresis and cyclic array sequencing offer such analytical capability, they identify in one read only 10-1000 sequential base pairs out of the total 3 Gb in the human genome. The complex repetitive nature of DNA makes it costly and time consuming to accurately reassemble a full genome. Recently, transmission electron microscopy (TEM) techniques[1,2] have been proposed that label specific DNA bases with heavy atoms and thus have the promise of significantly extending the length of individual reads. However, the accurate determination of the complete DNA sequence is complicated by the need for labeling and radiation damage that leads to read errors and limits the usable electron dose.

This paper describes the concept of a novel electron microscope technique capable of imaging a DNA base sequence of unlimited length at low cost with the high accuracy needed for full-scale sequencing. In this technique, two beams illuminate the sample with electrons having energies from 0 to several 100 eV, and the reflected electrons are utilized to form a magnified image (Fig. 1). The use of low energy electrons for imaging ensures that no radiation damage occurs, so high electron doses critical to achieving high throughput can be used. Dual beam illumination mitigates the charging effects occurring when insulating samples are imaged in an electron microscope[3]. The microscope includes a monochromator, which significantly improves spectroscopic resolution, and an aberration corrector, needed to achieve sub-nm resolution, a 10x improvement when compared to state-of-the-art LEEMs. This technique has the potential of delivering images of unlabeled DNA with nucleotide-specific contrast at high throughput and low cost, and will find a wide range of applications in the biosciences, material sciences and nanotechnology where nanometer scale resolution and analytical capabilities are required.

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[1] Glover, III; W. R., U.S. Patent No. 7,604,943, October 20, 2009.

[2] http://www.halcyonmolecular.com

[3] M. Mankos, V. Spasov and E. Munro, Adv. Imag. Elec. Phys. 161, p.1-54 (2010).

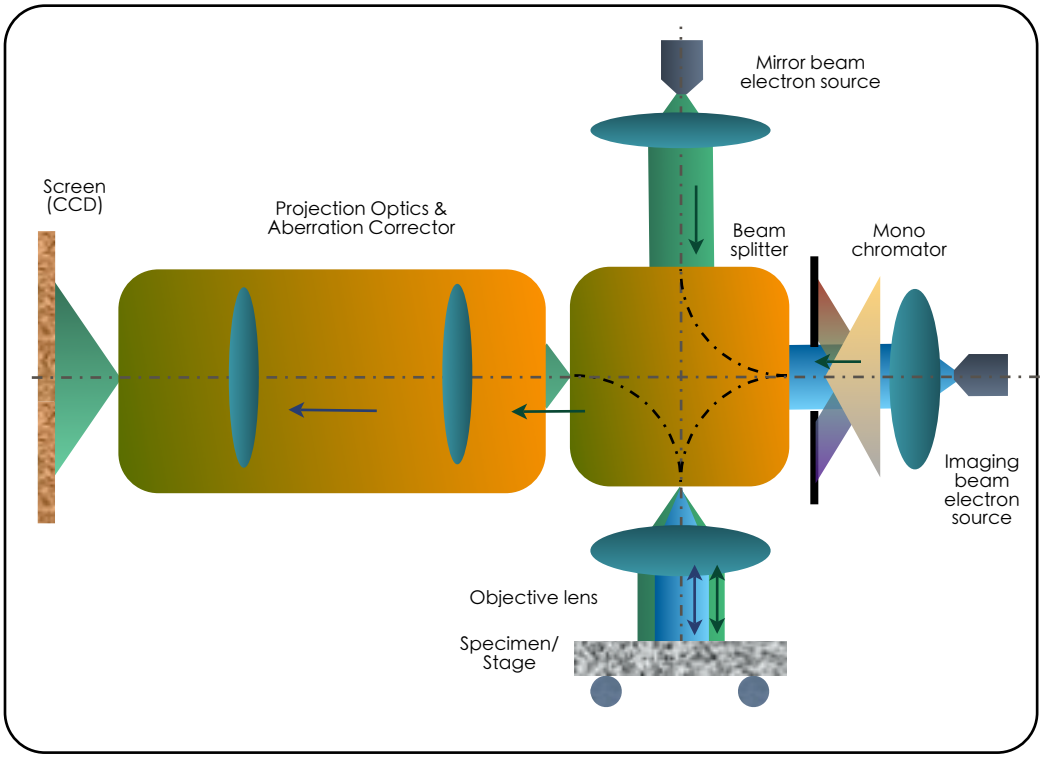

Figure 1: Electron-optical layout of a novel low energy electron instrument for DNA sequencing and surface analysis.