The project had three major aims:
1. Improvement of technology for high-speed cell and chromosome sorting;
2. The use of such instrumentation in genome analysis;
3. Apply the principles developed and the lessons learned to automated processes for the genome program.

The work was a continuation of studies that were started at the Lawrence Livermore National Laboratory before the PI moved to the University of Washington. At Livermore, a high-speed sorter for the selection of human chromosomes was built. The instrument incorporated Livermore's advanced sorter technology. The engineering focused on improving robustness and reliability so that the full potential of high-speed sorting would become available to the biological research laboratory. The new instrument, dubbed MoFlo for modular flow cytometer, proved to be a very practical and efficient tool during the chromosome isolation phase of the gene-library project. Its reliability and ease of operation exceeded that of the commercial instruments. The technology was licensed to two companies. Systemix, Palo Alto, CA, realized the instrument's advantages for the purification of stem cells for bone marrow transplantation and licensed the instrument for in-house use. Cytomation, Fort Collins, CO, decided to manufacture the instrument for the research market.

PI's move to Washington, in 1992, was instigated by several reasons. The environment in the national laboratories is an excellent environment for development of technology. Exploration of new uses and optimization for bio/medical applications requires an environment driven by biological rather than technical problems. The founding of the department of Molecular Biotechnology at the University of Washington by Leroy Hood, provided a unique opportunity to apply the new sorting technology to a variety of biological studies thereby testing its usefulness beyond chromosome sorting. DOE acknowledged these possibilities by funding the establishment of a flow sorting development / application group at the new department.

The program at the University of Washington has been very successful. The use with different biological systems has led to a great number of technological improvements. All electronic functions are now controlled by computer. The alignment is greatly facilitated which diminishes the requirements for highly skilled personnel. The overall lay-out is simplified and can easily be cleaned and sterilized. The latest embodiment of the instrument is divided over two rooms. All equipment requiring regular adjustment and repairs is located in a "machine room" to which technicians in "street clothes" have ready access. The part of the instrument that is in contact with the cells is located in a GMP (good manufacturing practice) environment and is operated by collaborators.
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wearing sterile gowns. This new set-up makes possible, for the first time, the responsible use of cell sorting to clinical applications. Systemix has obtained FDA approval for use of this instrument in clinical studies. The University of Washington is building a gene therapy lab in which the clinical-grade sorter will play a dominant role. These developments show that one of the major aims of the program: the transfer of the technology from the research lab to the clinic, has been achieved. his part of the program is now adequately supported by industry and no longer requires DOE support.

An advance sorting facility that has been built in Seattle and is used in a variety of programs. Barbara Trask and Ger van den Engh have used the instrument in the study of gross polymorphisms in human chromosomes. The use of the instrument has spread to other studies. Groups sorting prostate cells, single sperm cells for PCR analysis, Drosophila embryos, bacteria labeled with green fluorescent protein, human chromosomes, and many other cell types regularly use the facility. Some of the studies may be found in the literature list. This "service" is now supported in part by an NSF center grant. The remaining costs are carried by the users. Like the technology development, this aspect of the program has become self-supporting and no longer requires DOE support.

The technical development program has attracted a number of talented molecular biology and engineering students. Cell sorters incorporate a wide spectrum of technologies: lasers and optics, high-speed analog and digital electronics, computer interfacing, delicate fluidics, etc.. The design of robust and user-friendly equipment poses a formidable engineering challenge. Students can select a favorite topic and can test and develop their skills in a "real-world" engineering project. This setting turns out to be highly motivating. Biology and engineering students work in teams and appreciate each other disciplines and approaches. This collaboration has resulted in remarkably elegant engineering solutions. The core technology is now covered by 10 patents. Six more are in progress. Licensing to industry is in progress.

The engineering skills that are now represented in the cell sorter group have extended to other automation projects. Presently under development are: a highly-automated phase-sensitive gel scanner (project in collaboration with Oxford GlycoSystems); development of a sorter nozzle for arraying beads with a combinatorial library for drug discovery (collaboration with Pharmacopeia); the fabrication of microstructures that trap DNA molecules by inducted dipole moments (supported by DOE).

The program has met its goals. The high-speed sorting technology has been made reliable and has been transferred to industry and the clinic. A prospering sorting facility has been established in Seattle. This facility is very productive in a variety of biological studies. The technical skills developed during this project are now used in the development of other instruments for automating genome research. Most of the activities are now self-supporting.
Relevant Publications
(including some from the early stages of the program that were carried out in Livermore).


Asbury C.L., van den Engh, G.J., Manipulation of DNA using non-uniform oscillating electric fields (submitted).
Patents

van den Engh, G.J., Particle separating apparatus and method, US Patent pending