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Cutting edge: Electronic counting of white blood cells

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For decades, one of the most commonly ordered tests in the doctor's office has been the cell blood count (CBC). Although simple and relatively inexpensive, this test is a very effective screening tool for a wide range of conditions. For example, a lower number of red blood cells could be an indicator for anemia and further investigations could identify the likely cause. A higher number of neutrophils could indicate an infection in progress, while changes in the number of lymphocytes could reveal some metabolic or proliferative diseases.

The origins of CBC are linked to the discovery of chemical cell stains in the middle of the 19th century and the count was usually done manually, under the microscope, on hemocytometer slides. By the middle of the 20th century, automated measurements of electric impedance across apertures were introduced to count red and white blood cells, and size distribution within the red blood cell fraction. Currently, blood samples from patients are examined mostly using automated flow cytometers, based on principles of fluorescence or light scattering measurements, and are capable of counting not only red and white blood cells, but also the different leukocyte subsets.

Current standards for CBC follow stringent requirements for quality control and other regulations and rely on automated machines located either in hospitals or centralized laboratories. While this system works well for most large hospitals, it leaves few options for smaller practices or family doctors, who have to deal with the logistics of sending the samples and handling the time delays between seeing the patients and receiving the results. Advances in technology could challenge the *status quo* and bring new tools into the doctor's office, for the immediate benefit and convenience of all patients, either visiting the doctor's office for regular checkups, signs of disease, or monitoring for chronic ailments. Towards this goal, lab-on-a-chip devices could not only help with the miniaturization of existing machines, but could accelerate the progress through the implementation of new detection and measurement principles.

In this issue of *Lab on a Chip*, a micro-fluidic device for counting white blood cells and differentiating the major subtypes is presented by Holmes *et al.*¹ Whole blood samples are quickly processed and then passed through a micro-channel with two pairs of microelectrodes that are used to measure the impedance of single cells. The originality of the design is in the use of two different frequencies to discriminate between major white blood cell subtypes. Lymphocytes are first identified at the first pair of electrodes, on the basis of the low frequency impedance signal and counted separately from neutrophils and monocytes. Further discrimination of neutrophils from monocytes is performed using both pairs of electrodes and the impedance signals at high and low frequencies. Customized

software analyzes the signals and provides a differential cell count, which is within 95% of the values from the same blood samples, available through state of the art instruments.

One of the most interesting features of the new prototype is the ability to perform the differential count based entirely on electrical signals. This approach would be optimal for robust point-of-care applications, and will avoid challenges common for all optical detection methods that add cost and complexity to detection systems (*e.g.* lensing, filtering, or focusing elements). This could reduce the costs per sample that is analyzed, and increase the availability of CBC in regions of the world where alternatives would be expensive, or the infrastructure of clinical labs is not yet developed.

Towards a simple and inexpensive CBC test, several challenges would have to be addressed. The sequential mixing of blood and reagents is now performed off the chip. This sample preparation step would have to be automated to avoid processing artifacts. The prototype presented in the paper can analyze 100 cells in a second and provide results starting with whole blood samples as small as a single droplet (50 microliters). At the same time, the results in the paper show that with increasing the number of cells counted the precision of the measurement improves. Consequently, it could be worth exploring ways to achieve higher throughput for cell analysis. Current technology can only differentiate between leukocytes, neutrophils and monocytes. Future developments would have to address the problem of other populations of white blood cells that are important in clinical diagnostic, *e.g.* eosinophils and basophils in allergies or parasite infections. Finally, larger scale testing of the device, including not only healthy volunteers, but patients with diverse diseases is a critical step towards validating the exciting potential of this new CBC analysis approach.

Biography

Daniel Irimia was educated in Romania as a medical doctor, received his PhD in Bioengineering from the University of Illinois at Chicago, and currently is an Instructor in Surgery and Bioengineering at Harvard Medical School. Dr Irimia is an expert in microfluidic tools for the quantitative studies of cell migration and the integration of engineering principles into biological research and medical diagnostics.

References

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