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Counting nanoparticles in real time

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They're difficult to detect and even harder to count but a team at the University of California in Santa Barbara has cracked the code, says s ananthanarayan

EVEN before the advent of nanoscience or synthetic nanoparticles, nature made effective and widespread use of the very small as mediators in complex physiological processes. On the other side of the fence are the viruses, with diameters less than 150 nanometers, which take millions of lives every year. But because such particles are too small to detect, any defence against viruses has to be by blanketing measures in affected areas, measures that affect the virus and healthy cells alike. In Nature, a multidisciplinary group at the University of California, Santa Barbara, reports on improved equipment that can detect and count nanoparticles as small as 10 nm.

"This device opens up a wide range of potential applications in nanoparticle analysis," says Jean-Luc Fraikin, lead author on the study. "Applications in water analysis, pharmaceutical development and other biomedical areas are likely to be developed…"

The first sally into detecting and measuring very small particles was perhaps in 1676 when Antoni van Leeuwenhoek discovered red blood cells under the microscope. The process has become routine in the pathology lab, where constituents of the blood or body fluids are studied for diagnosis and therapy. Estimates of population of target organisms are typically made by physically counting the numbers of instances in a marked area in the field of view. But this method, apart from being approximate and subjective, is also only good for particles that are visible in the microscope. For the smaller scale, nanometer level particles, the method of choice was dynamic light scattering, where the intensity and frequency of light scattered by a sample provides information of the quantity and size distribution of suspended particles.

Another method is disk centrifuging, where the sample is spun inside a stack of conical disks and components are separated in the space between disks. But these methods are slow, cumbersome and call for sizeable samples of the fluids under study. Individual nanoparticles can be studied under the electron microscope, but this is hardly practical at the routine level and these methods are not successful when the particles to detect are present in small numbers.

An indirect method that has been used for over half a century is the Coulter counter method. In this, there is a microscopic aperture in an insulating membrane. An electrical gradient is applied between the two sides of the membrane, which is immersed in a conducting liquid. As the membrane is an insulator, any current can flow only through the aperture, and this current is measured. Now, if there are cells or other particles in the liquid and one of them passes through the aperture, it will effectively block the current path while it is passing through, which would register as a drop in the current. Such

changes in current strength are detected and counted to provide data of particle movement.

The Coulter counter has become an important tool in hospital laboratories, primarily for quick and accurate analysis of Complete Blood Counts, which shows the number or proportion of white and red blood cells in the body. The traditional method was to prepare a blood cell stain and manually count each type of cell under a microscope, a process that could take half an hour. Coulter counters are now used in different fields, like paint, ceramics, glass and food manufacture and for quality control.

The same principle is used in the nanopore, which can detect much smaller particles like DNA or protein molecules. The insulating membrane could be a double layer of oil-like molecules, with the pore being a local modification in the molecular structure, to work as a protein channel. It could also be a protein channel planted in a synthetic membrane or a physical hole in a solid laminar membrane.

But while these methods have been useful in the fields where they were developed, they are cumbersome and cannot provide rapid count rates, which is required in many nanoparticle characterisation applications.

Santa Barbara analyser

The arrangement developed by the Santa Barbara group allows a rapid and automated count of up to half a million particles every second, simultaneously measuring the volume of each particle to keep count separately of different types of particles. The arrangement is a version of the Coulter counter and combines a simply fabricated passage for the fluid, under an electric field and provided with a nanoconstriction, and a detector of the electric resistance of the arrangement.

Every time a particle passes through the constriction, the electric path is blocked and the sensor picks up the drop in current. The signal is electronically processed, for count as well as the size of the particle, from the extent of the drop in current. The arrangement can be configured to provide very rapid response, with precise size measurement, for analysis of complex mixtures. The arrangement has been able to detect virus particles suspended both in saline solution as well as in blood plasma.

Measurements on blood plasma have revealed a vast number of smaller sized nanoparticles, probably cell-derived bubbles of material, called vesicles, which are thought to be involved in different physiological and pathological processes. Earlier studies of these particles required extensive sample preparation and purification, for electron microscope study. Use of the Santa Barbara analyser permits speedy and detailed study with minimal preparation, which is a study of the plasma particles in their native state.

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