

# Medical Imaging Monitors Pharmaceutical Process Health

Tomography is widely used in medical imaging, but also is becoming a useful PAT tool for process development and optimization. In this article, Ken Primrose, principal of Industrial Tomography Systems, discusses electrical resistance tomography (ERT) and its implications for pharmaceutical manufacturing.

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It's relatively easy to get on-line data from a point source in a process vessel. But the data are of little value unless your liquor is homogeneous, so that the sensor sees a representative sample of the contents. And how do you know if you have perfect mixing? Scanning the whole volume would be much more valuable, and that's just what a new technology – electrical process tomography (ERT) – does.

The FDA's encouragement of science-based approaches to production control (under its Process Analytical Technologies initiative) is a great stimulus for such innovative ideas. Where process conditions in a vessel vary, using ERT to get spatial rather than point-based information can make a big impact on process control and optimisation.

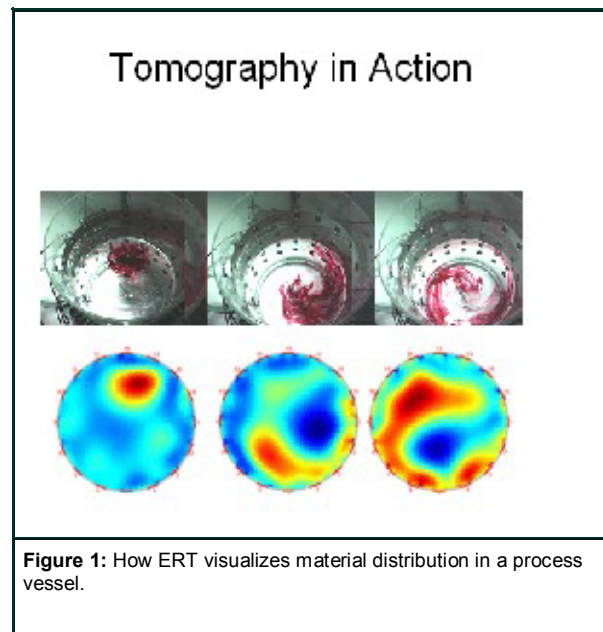
ERT is the process industry equivalent of whole body scanning in a medical environment. It is non-intrusive and has no moving parts. Industrial Tomography Systems (ITS) of Manchester, UK – a spin-off from the University of Manchester – is developing the technology as a PAT tool. It has on-going projects under confidentiality agreements with a range of international companies, amongst them some giants of the pharmaceuticals industry.

## How the technology works

What does ERT look like in action? It is fundamentally a simple sensor network coupled with highly sophisticated electronics and software. Imagine an array of electrodes – typically 16 – arranged in the same plane on the inner circumference of a process vessel. If you then apply a small AC current very rapidly between a pair of electrodes, the resultant voltage difference between remaining electrode pairs can be measured according to a pre-defined measurement protocol. Then apply current through the next pair of electrodes and repeat the voltage measurements. And so on.

An image reconstruction algorithm, the heart of ERT, provides amongst other things an image of the distribution of materials in the sensing volume (see Figure 1, above). Add other sensor arrays and you can view the situation throughout the whole vessel.

How many measurements and how fast? In the course of some 25 milliseconds a 16-electrode sensor gives 104 independent measurements – enough to get a real-time picture of the conductivity of the process fluid in that volume. Conductivity can be related to many physical properties, and in particular to the concentration of different components.



## Practical probing

Placing electrodes around the internal surface of a vessel may be a rather laborious use of resources. So ITS worked on an alternative. Inserting electrodes along the length of a probe (Figure 2, at right) creates a much more versatile piece of equipment which can be lowered into a vessel in place of an existing baffle. A probe can be used across a range of vessel sizes. Of course the image reconstruction algorithm needs appropriate adjustment for the new disposition of electrodes, but the result is a similar real time image of the contents of the whole vessel.

In various cases, electrode deployment matches other practicalities of the situation. To picture fluid flow in a pipe, the most appropriate array is similar to that around the internal circumference of a vessel. In a hydrocyclone the inside wall is again the position of choice, but with a graduated diameter. In pressure filtration, which is described later in this article, arranging them across the filter bed proves least obtrusive.

## And how would you use it?

All sorts of applications spring to mind. Throughout the pharmaceutical industry there is a need, for instance, to ensure good dispersion of solids in liquids or to observe separation of organic and aqueous phases. Current technology is limited in what it can tell you. ERT allows you to watch the mixing characteristics of the process vessel contents while you adjust conditions to improve them (Figure 3, below).

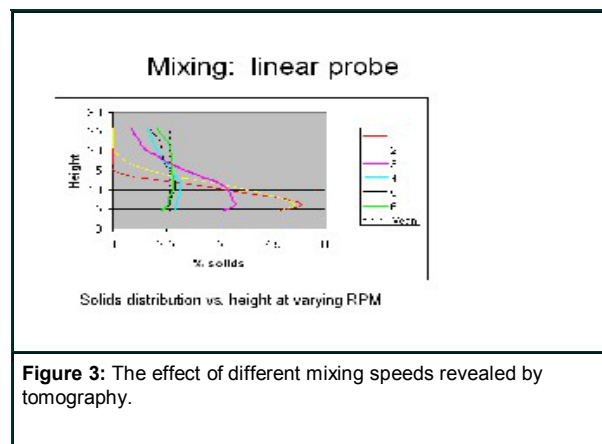
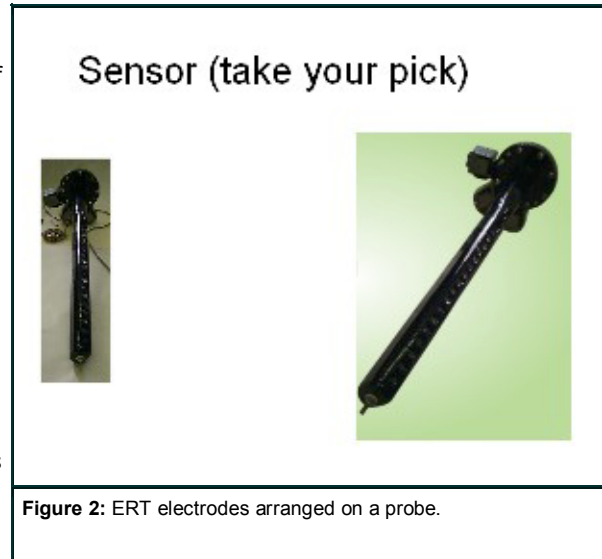
Crystallization is another process well suited to monitoring by ERT. When two ionic species in solution produce a salt, the difference in signal between salt and solution is rather large. This means that ERT is very sensitive to the onset of crystallization. Analysing the dissolution of slow-release capsules is another potential application. These capsules are meant to let drugs out slowly into the body from the stomach and have been in the news recently ([www.pharmacist.com/articles/h\\_ts\\_0747.cfm](http://www.pharmacist.com/articles/h_ts_0747.cfm)). During proving tests in a "simulated stomach," ERT could provide a clear picture of how salts are released from a tablet.

## As a substitute for tradition

Pressure filtration is an acute example of a process needing quality on-line monitoring. At the moment, there is little or no on-line help in determining end point or assessing filter cake homogeneity. Traditional methods are basically empirical. Filtration routinely continues far too long, wasting time. And there is no satisfactory way to spot formation of rat holes in the filter cake.

With UK government backing, ITS suggested ERT for trials as a PAT tool to leading bio-processor Syngenta and filter manufacturer Rosenmund. In this case, 24 electrodes were used and arranged, with careful regard to filter integrity, in two distorted rings of eight and 16 across the filter cloth hold-down bars of a 36m<sup>3</sup> vessel. Experts in electrochemistry from Glasgow Caledonian University kept a critical eye on product integrity.

ERT data (Figure 4, below) allows comparison of filtration batches. The step increases and



decreases in resistance during the early stages of each batch show the various wash cycles. The steady increase in resistance in the later stages corresponds to the drying cycle. Each data point on these graphs is a mean of over 100 individual voltage measurements taken from different regions within the filter, making the data sets amenable to statistical analysis.

The potential benefits of using ERT to monitor pressure filtration? Better control and planning, meaning that management knows when filters should be available for use and can take early action when a bad batch is being processed. In addition, process efficiency can be improved through more effective manufacturing and capital savings are possible through more effective asset utilisation.

### **Benefits summary**

ERT is adept at picking up regional variations and changes, which are very important to know about when you are dealing with complex reactions or scale-up. It can also add value to existing measurement technologies. As a resource, it provides statistics both over space, showing variation within a specific region, and over time, plotting the trend towards an end point.

To summarise other features of the more general use of the technology:

- The visual material supplied by ERT allows you to understand better what is going on in your process.
- The visual information can be reduced to key statistics (for instance, variance).
- Adjusting conditions on the basis of visual information means shorter lead times, and that helps you make better use of your assets.
- Better control of the process leads to bigger yields of the product you desire.

On ease of use:

- The equipment is scalable from laboratory use to production.
- Mounting the electrodes on a probe makes ERT easy to retrofit, simply replacing a baffle.
- Experience suggests the equipment is robust and intrinsically safe.
- ERT lends itself to a range of solutions from polar organics to strong acids and bases.
- It works for pipes as well as vessels.

### **ERT as a process tool**

Industrial Tomography Systems has been working alongside major pharmaceutical companies on the development of the technology for use on process plant. This has included developing the instrumentation to comply with the requirements of intrinsic safety certification for operation in flammable atmospheres, sensor developments (electrode architecture and materials of construction) to allow retrofitting to existing process vessels and operation within chemically aggressive environments.

ERT in various guises is providing information on the actual performance of manufacturing processes and insights into process dynamics that influence product quality and manufacturing performance. It can provide a fundamental understanding of the manufacturing processes. And there is every sign that ERT will become a standard PAT tool.

For more information, contact Industrial Tomography Systems ([www.itoms.com](http://www.itoms.com)).

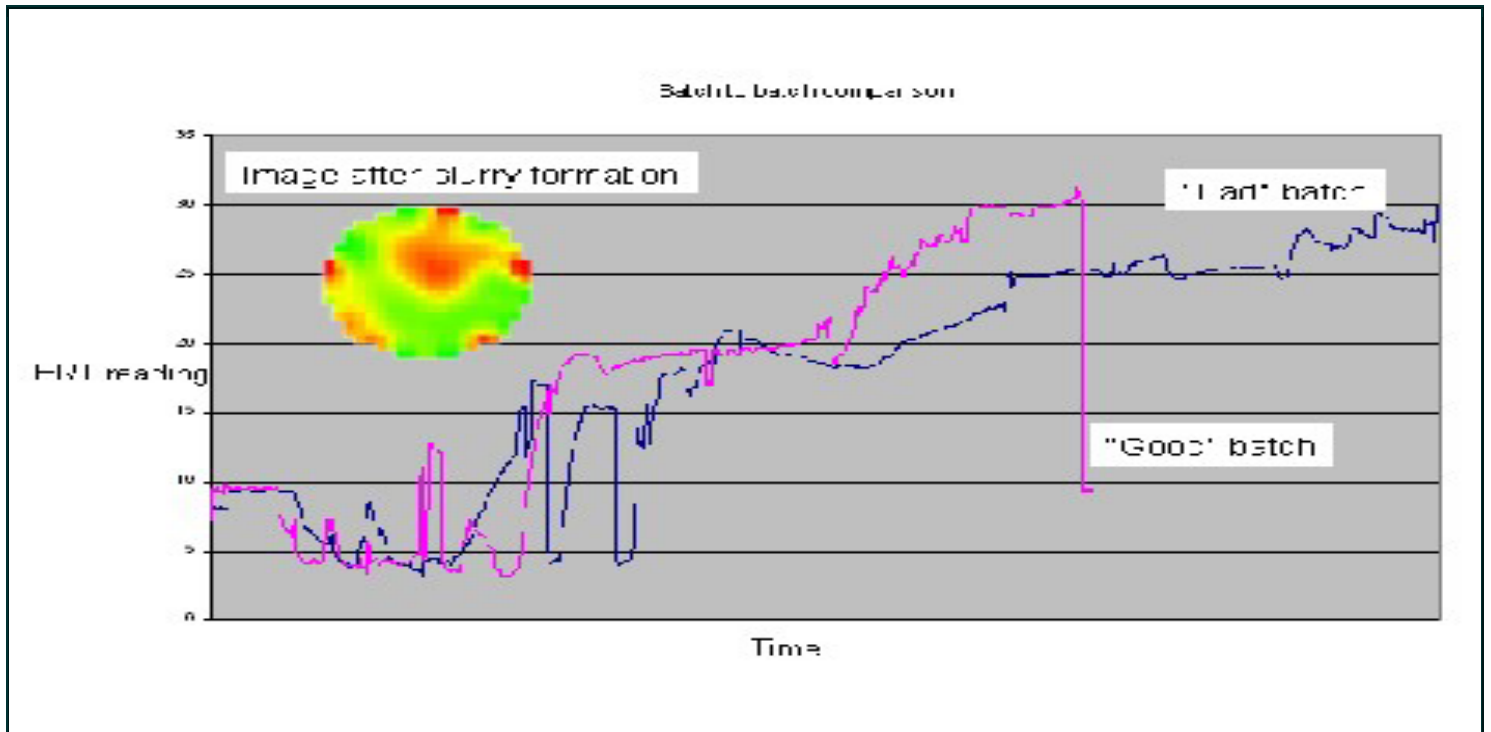


Figure 4: ERT reveals bad pressure filtration batches at an early stage.