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Recent developments in electrical resistance tomography for the pharmaceutical industries

ABSTRACT
Although process tomography is still in its infancy, the capability to image the interior of process units in 3D is expected to become an important component in PAT in the future. Some recent developments in electrical resistance tomography (ERT) are reviewed. Illustrative images of mixing in stirred vessels and conductivity distributions in wet filter cakes are presented in various computer graphic formats. The potential of process tomography to promote innovation from the conventional stirred batch reactor is highlighted. In future improved process imaging will result from combining more than a single modality, for example ERT combined with x-rays, t-rays, optics, acoustics, or MRI.

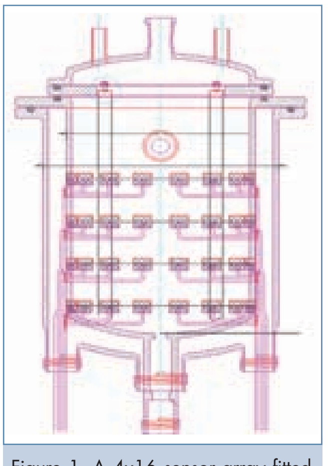

Figure 1. A 4x16 sensor array fitted in a glass vessel (Ricard et al (2)).

INTRODUCTION

Process Analytical Technology (PAT) has a key role to play in improving the underlying "science" of much of process engineering. Previous largely conservative design and scale-up policies, plus a regulatory framework which historically imposed precise replication of process steps, has left the pharmaceutical industries apparently trailing behind more modern looking industrial sectors like electronics. Hence, many manufacturing facilities look like simple geometric scaled-up copies of common laboratory equipment like beakers and filters.

What is needed to improve manufacturing is a framework encouraging innovation in the process technology which is soundly based upon clear understanding of the underlying process fundamentals (1).

One key element crucial to pharmaceutical manufacturing is the measurement of concentrations, especially for control of reactivity and reaction rates. Furthermore, a few single point measurements will be inadequate when concentration fields vary in both space and time.

Such measurements should also be fast and non-intrusive/invasive. For industrial adoption, any instrumentation must also be inexpensive. This review gives details of some recent developments in capabilities for 3D imaging of concentration within reactor vessels and filters widely used in manufacturing. Electrical process tomography is still in its infancy, but offers huge potential for delivering process understanding, especially as computing speed and power continue to advance.

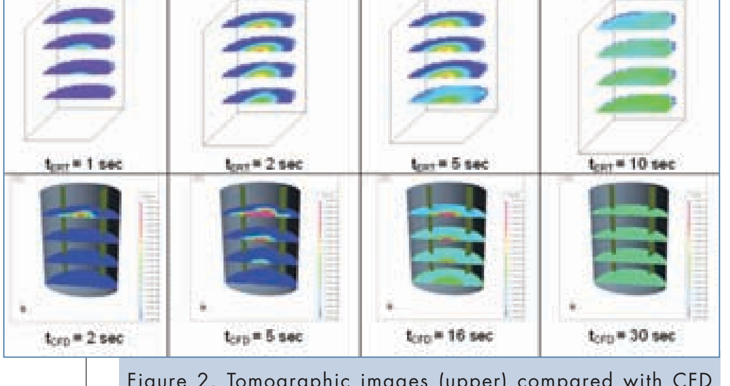

Figure 2. Tomographic images (upper) compared with CFD predictions (lower) for tracer fluid mixing using a retreat blade impeller (Ricard et al (2)).

IMAGING OF A GLASS STIRRED VESSEL (PFAUDLER)

Whilst electrical tomography had been under development as a research tool since the mid-1990s, mainly based on plastic walled vessels, in 2003 Ricard et al at GlaxoSmithKline first pioneered direct application into pharmaceutical R&D (2). The emerging technology and its associated instrumentation (from ITS, a Manchester University spin-out company) was ideally suited for evaluation on a typical glass vessel widely encountered in pharmaceutical manufacturing. A cylindrical vessel equipped with a Pfaudler retreat-blade impeller was fitted with a 4x16 sensor array as shown in Figure 1. In this configuration, the platinum sensor plates fitted flush into the glass walls and are therefore completely non-intrusive and do not interfere with the flow and mixing generated by the rotating impeller. Current (milliamps) is injected sequentially between all sensor-pair combinations in each horizontal circular array and the corresponding sensor-pair voltages (millivolts) are detected for each injection.

This interrogation of the electrical field at the boundary in each of the four planes allows the image reconstruction of the electrical field across/within the plane. Figure 2 shows sets of images from linear back-projection presented in a colour contour format for each of the four planes. The tomographic images are for the injection of a brine tracer (high conductivity) in tap water (low conductivity) and the dynamics of the fluid mixing can be clearly discerned as the tracer mixes in three dimensions.

These are referred to as pseudo-3D images because any out-of-plane conductivity is neglected in the interpretation. Nevertheless, as Figure 2 shows, the tangential swirling and the axial-radial convection of the conducting tracer are

impressively captured in space and time.
In Figure 2 there are 104 measurements between the 16 electrode plates in each ring and therefore a total of 4x104 measurements available to reconstruct the conductivity/concentration field in (pseudo) 3D.
Also shown in a similar format in Figure 2 are some computational fluid dynamic (CFD) predictions obtained by solution of the fluid mechanics. Although the correspondence in this case is not perfect, the electrical tomography field provides a density of information which allows for a more profound basis for validation of the CFD. These evaluations will enhance understanding of the complexities of fluid mixing and their role in determining the performance of stirred vessel reactors when used in pharmaceutical drug manufacture. In other words, electrical tomography clearly has an important future role to play in PAT and progress towards Quality by Design (QbD) for pharmaceutical chemical reactions. More complete details of this pioneering development, including evaluation for a simple esterification reaction are available (2). Also, in a subsequent paper, the authors disclosed results for a somewhat simpler linear sensor array capable of detecting variation of solids suspension density in a similar stirred vessel (3).

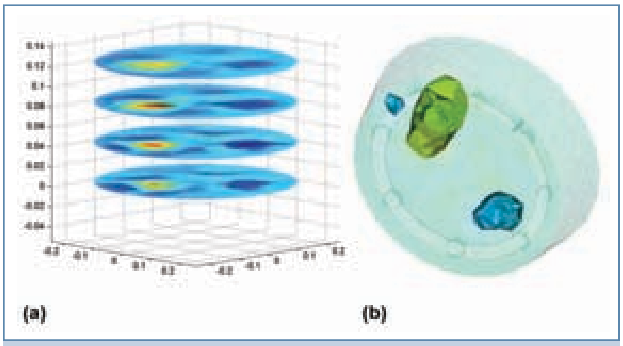

Figure 3. Image reconstruction of phantoms in a filter cake for (a) planar tomogram stack and (b)solid body imaging in 3D.

IMAGING OF A FILTER CAKE

In general, there are many possible variations for interrogation of the process space using electrical resistance tomography. The set of four axially spaced planes used for the stirred vessel in the earlier Figure 1 provide an obvious capability for creating 3D images of the interior volume. However, somewhat surprisingly, it turns out that it is nevertheless possible to reconstruct in 3D from a set of measurements acquired solely from a single plane. This has been convincingly demonstrated by Davidson et al. (4) for a filter vessel. Figure 3 thus illustrates how the measurement and reconstruction can work in this very typical pharmaceutical process device. The results depicted are for a 1 metre diameter pilot scale filter with an approximately 10cm thickness of filter cake. Embedded in the cake are two small cylindrical vertically aligned "sponges" one soaked in water and the other in strong brine. The wet cake has an intermediate conductivity corresponding to weak brine. In this example, there are just eight small sensor discs arranged radially on the base of the filter plate (beneath the cloth) which can be seen in Figure 3(b). This configuration could be termed an 1x8 array, as compared to the 4x16 array for the previous stirred vessel. As described for the stirred vessel interrogation, in this case each of the possible pair combinations are subjected to current injection/voltage detection so that the whole volume of the cake experiences measurement as the different electrical fields are applied. Figure 3 then shows two cases for visual representation of the reconstructed conductivity (hence ion concentration). On the left in Figure 3(a) the fields are presented as four colour contour planes (also called a stack of tomograms) with the high conductivity showing red and the low conductivity blue. This clearly demonstrates that the electrical resistance tomography set-up reveals the presence of the two phantoms, which are otherwise invisible within the cake. In Figure 3(b), two solid-body contours are drawn for high and low conductivities thus locating the two phantoms.
This capability is available for monitoring 3D concentration fields within filter cakes whilst they undergo washing/drying, and thereby offers a powerful capability for monitoring and control.

FULL-3D IMAGING OF A STIRRED VESSEL

As computing power increases, process tomography is expected to develop faster and more intelligent and optimised interrogation protocols concurrently with improved accuracy and veracity of the reconstructed 3D images generated from the non-invasive peripheral sensing. A great deal of work is going on in the development of the relevant mathematics of reconstruction. Figure 4 shows some recent results (Stephenson (5))comparing a hierarchy of reconstruction possibilities applied directly to a real time process observation rather than the static phantoms of the previous filter cake illustration. The process is again the mixing of a high conductivity tracer in low conductivity tap water, in this case taking place in a 0.6m baffled vessel stirred at 105rpm by a Rushton turbine. The images in Figure 4 show six example reconstructions from the (single) voltage set collected some 0.9 sec after initial tracer injection.
The caption to Figure 4 refers to (a) which is the standard 2D linear back projection (LBP) algorithm supplied by ITS with their P2000 electrical tomography instrument, (b) is the 2.5D LBP method also supplied by ITS, (c) is true 3D but still linear back projection. Linear algorithms are not expected to furnish perfect accuracy reconstructions because of the intrinsically non-linear so-called "soft" electrical fields. They are however usefully fast and can be used to image in real time. On the other hand, the soft-field non-linearity imposes some severe computational burdens for the three non-linear algorithms in Figure 4 which use (d) Landweber, (e) conjugate gradient and (f) generalised singular value decomposition (GSVD). Stephenson's study (5) lays the basis for further investigations simply because the six possible techniques tend to produce relatively wide and significant variation in the shape of the "cloud" of tracer as it convects and mixes. Validation is needed so that confidence about the interior vessel concentration fields in 3D can be improved, enabling more reliable reactor designs to be formulated.

INNOVATION BEYOND TRADITIONAL BATCH REACTORS

PAT by providing instrumentation for better characterization and understanding should promote sound innovations that

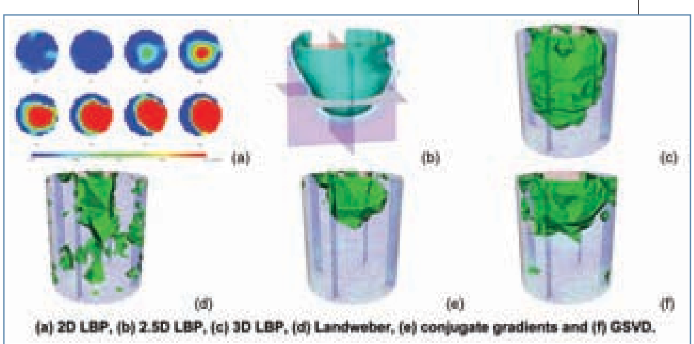

Figure 4. Effect of reconstruction method on vessel plume images.

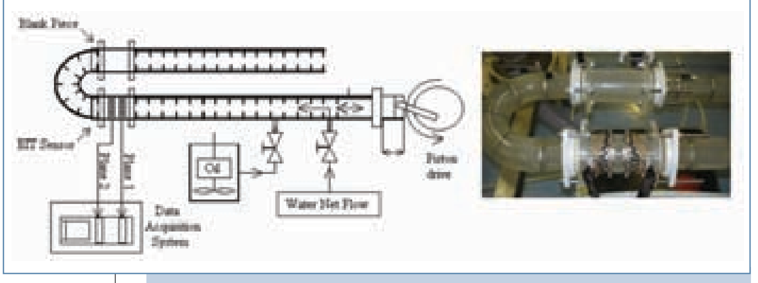

Figure 5. Oscillatory baffled flow reactor (OBR) fitted with ERT tomographic sensors.

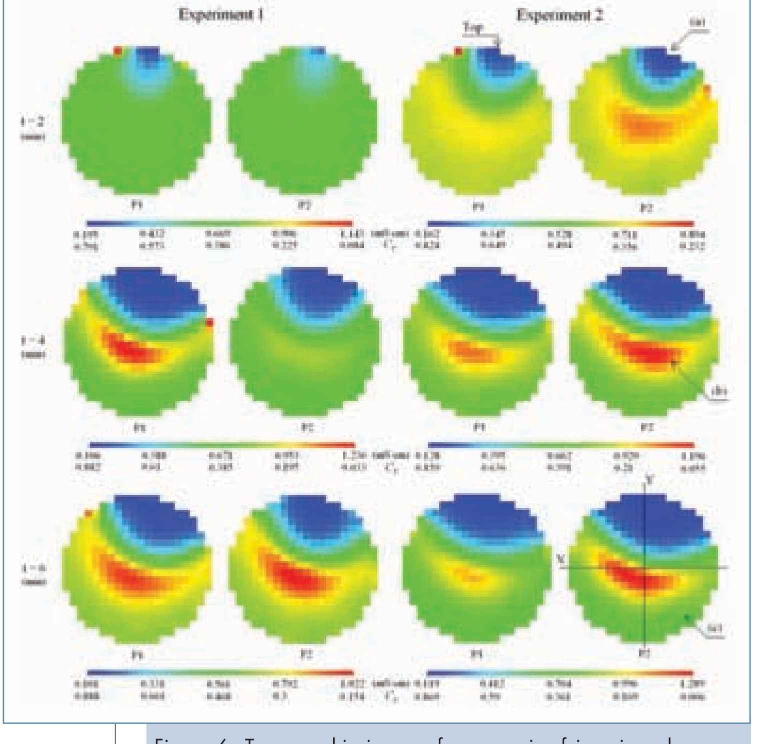

Figure 6. Tomographic images from a pair of imaging planes on OBR.

would enable the process technology to progress beyond the "conservative" use of stirred vessels (which resemble a simple geometric scale up from a laboratory beaker). A clear possibility is improvements in inventory control and product handling from the use of continuous flow instead of batch operation.

There are many examples of applying electrical tomography to pipeline flows. For example Wang et al (6) have investigated the solids concentration at various positions downstream of an in-pipe swirl flow inducer device in a hydraulic conveying operation. Thus the technology is well positioned for continuous flow application.

A recent application of electrical tomography to a novel continuous flow reactor has shown how tomography can promote innovation (7). Continuous flow reactors also offer the potential to increase yields, reduce waste, provide greater control of particle formation, improve control over size distribution and increase heat and mass transfer.

This study applied electrical tomography to measure the complex flow pattern in an Oscillatory Baffled Reactor (OBR) shown in Figure 5. The main characteristic of the OBR is that an oscillatory movement is superimposed on the process fluid moving through a tubular reactor with regularly spaced annular baffles.

The oscillatory movement coupled with the baffles enable the formation of eddies on either side of the baffles creating significant radial motion and thus effective mixing. With the OBR, conditions very close to plug flow can be achieved at relatively low flow rates, resulting in consistent product quality and reduced waste. Figure 5 shows two 16-electrode sensors rings installed on the pilot-scale OBR. The work demonstrated how the flow pattern was related to critical product information such as droplet size for an oil-water emulsion, although this could equally be applied to a crystallization process. The sets of tomogram slices in Figure 6 show how effective the system is at visualizing the mixing.

THE FUTURE

Imaging of fluids in the interior of process units will undoubtedly make a growing contribution to PAT in future. In this review, a few simple examples have been highlighted based upon electrical resistance. This is only one of many so-called tomographic modalities.

Other electrical modalities include, capacitance, impedance (a combination of resistance and capacitance) and electromagnetic inductance. Aside from electrical techniques, wider modalities include x-rays, terahertz-rays, optical, acoustic and NMR. In future there will be improved imaging from combining modalities, a key way of eliminating uncertainties from the reconstruction mathematics. A useful snapshot of current R&D in most of these modalities, with glimpses of many new developments in the future can be gleaned from the Proceedings of the 5th World Congress in Industrial Process tomography held in Bergen in September 2007. These Proceedings are available through the Virtual Centre for Industrial Process tomography (www.vcipt.org).

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