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An Overview of Electrical Tomographic Measurements in Pharmaceutical and Related Application Areas

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ABSTRACT

Tomographic measurement techniques offer the opportunity to quantify the degree of homogeneity of particulate suspensions and other multiphase mixtures. Electrical resistance tomography is a relatively simple and inexpensive technique for measuring the distribution of electrical conductivity within multiphase systems. This can provide pertinent information about the physical form, the chemical composition, or the general status of manufacturing. In this contribution, we present recent applications of this technology to processes in pharmaceutical and related application areas. Examples include on-line measurement of solids distribution in stirred tanks and crystallizers, monitoring the performance of an industrial pressure filter, and flow profile and velocity measurements in a physical model of a catalytic reactor.

KEYWORDS: tomography, process, electrical, mixing, crystallization

INTRODUCTION

Process tomography offers the opportunity to visualize the contents of vessels and pipelines containing multiphase mixtures without disturbing the flow.[1] In the case of electrical resistance tomography (ERT), multiple electrodes are arranged around the periphery of the process vessel or pipeline in such a way that they are in contact with the process fluid but do not disturb the process flow pattern. A small alternating current is applied between electrode pairs, and voltage measurements are made between remaining electrodes pairs according to a predefined measurement strategy. A 16-electrode sensor delivers >100 independent measurements (the exact number depends on the measurement strategy) in approximately 25 ms. An image reconstruction algorithm is used to generate images of the distribution of materials within the sensing zone. ERT is a simple and robust measurement technique with a wide range of research and development applications demonstrated, including interrogation of mixing processes,[2] investigating a solid-liquid filtration process,[3] monitoring the performance of a hydrocyclone,[4] and measurement and control of bubble columns.[5] The most common electrode architecture is circumferential mounted electrodes, typically around a process vessel or pipeline. However, examples will be discussed where other electrode architectures were necessary to allow retrofitting to existing processes in such a way that the process efficiency and vessel integrity is not detrimentally affected.

Tomographic measurement techniques differ from point measurement techniques, because they sample a substantial proportion of the process volume rather than at a single point. Circular pipeline-based sensors measure an entire cross-sectional volume. Figure 1 illustrates the "sensing zone" for a linear sensor mounted within a stirred tank. Industrial Tomography Systems (ITS) is at the forefront of the transfer of this technology from the research laboratory to industrial plants. These measurements can give information on the performance and status of the manufacturing process, as well as important insights into the dynamics of the process. In this respect, electrical resistance tomography falls under the umbrella term of process analytical technologies.

Application of ERT to Pressure Filtration

Pressure filtration is commonly used to separate a solid fraction from a liquid phase. The liquid and solid mixture is typically agitated within the filter. The agitator is removed from the homogenous slurry, and the unit is pressurized. A liquid outlet valve is opened to allow the liquid phase and fine particulates to pass through the filter mesh leaving the remaining solids in the form of a filter cake. It is usually important that the cake forms uniformly as the mother liquor drains through it, because this ensures an even distribution of voidage in the cake within which some of the mother liquor will inevitably be retained. This is particularly important if the filter cake is subsequently washed with a solvent to ensure uniform rinsing so that any traces of the mother liquor are effectively and efficiently displaced. After the filtration steps, the filter cake may be dried by blowing air through the vessel before the cake is finally removed. Again, the uniformity of the cake is important to ensure that drying of the cake does not leave unevenly contaminated regions of particulates.

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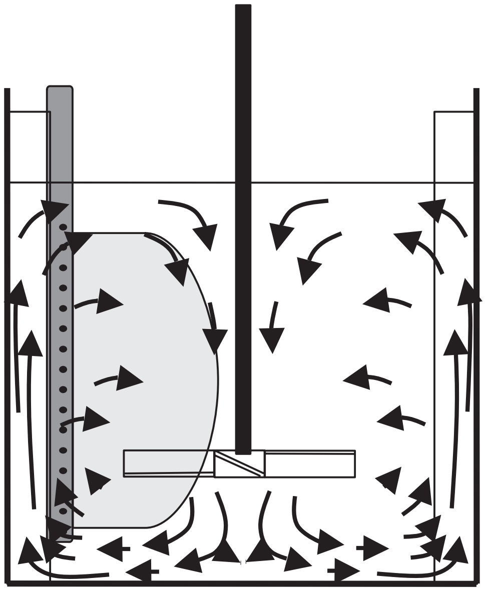


Figure 1. Illustration of sensing zone for a linear sensor in a stirred tank.

ERT was first applied to a pressure filtration during a 3 year United Kingdom government-backed Foresight Process Tomography partnership during 1997 to 2000 between academia and industry. Grieve et al[6] discuss a feasibility study on applying ERT to a commercial 1.5 m^3 pressure vessel. A temporary 16-electrode ring ERT sensor was fitted to the filter, and brine slurry was filtered under a pressure of 1 bar(g) nitrogen for approximately 2 hours. After drying, the cake was rewetted with brine via a single entry point, and filtration was repeated several times. Image reconstruction was performed by linear back projection. Validation of the results was not possible; however, the images clearly showed a feature corresponding to the position of a crater caused by the brine feed point, which could be viewed through the sight glass in the top of the vessel.

Vlaev et al[3] describe solid-liquid filtration monitoring by means of a 16-electrode ring ERT sensor on a 1-m diameter semitech scale filter. ERT was found to measure the conductivity changes accompanying the rise and fall of liquor level above the filter cake. In addition, on image reconstruction by linear back projection, the image showed a loss of symmetry if the ERT sensor is displaced from the horizontal. The ERT sensor can, thus, provide potential information on correct assembly and ongoing mechanical integrity of the filtration system. ERT was also demonstrated to detect malformation and unevenness in a forming filter cake.

Grieve et al[7] describe a scale-up of this application to a 36-m^3 production pressure filtration vessel at the agrochemicals manufacturing site of Syngenta Ltd (Huddersfield, United Kingdom). The stated purpose of the work is to provide real-time information on end point of filtration and drying, imperfection in the filter cake, and solvent displacement of the mother liquor.

The pressure filter was located in a flammable atmosphere and handled chemically aggressive material. It was necessary to retrofit an ERT sensor to the unit, and this presented a number of challenges. The first of these was the design of a system that met the requirements of Intrinsic Safety certification, which was achieved by the use of zener barriers to limit the power that could be delivered to the electrodes located in the hazardous area. Remaining challenges included the electrode materials and design, cable routing and exit detail, and some operational constraints. This study demonstrated that an ERT sensor could be retrofitted to a large pressure filter without the need to modify the internal structure of the unit. It also demonstrated that ERT could be certified to comply with intrinsic safety regulations rendering the technology suitable for the most hazardous of flammable atmospheres. The design of the electrodes suffered from a number of weaknesses, which were resolved through a number of design iterations.

The application of ERT to pressure filtration continued through funding from a United Kingdom Government LINK initiative from 2001 to 2004 involving Syngenta Agribusiness, Rosenmund (De-Dietrich), ITS, University of Manchester Institute of Science and Technology (United Kingdom), and Glasgow Caledonian University (United Kingdom).

Figure 2 shows some recent data collected using an intrinsically safe version of the ITS P2000 ERT system. The data shown are the mean resistance of the pressure filter contents. The various wash cycles are indicated by the step increases and decreases in resistance during the early stages of each batch, and the drying cycle is indicated by the steady increase in resistance. It can be seen that the initial filtration step and subsequent wash were of a much longer duration for one of the batches. It is worth noting that each data point on these trends are a mean of >100 individual voltage measurements taken from different

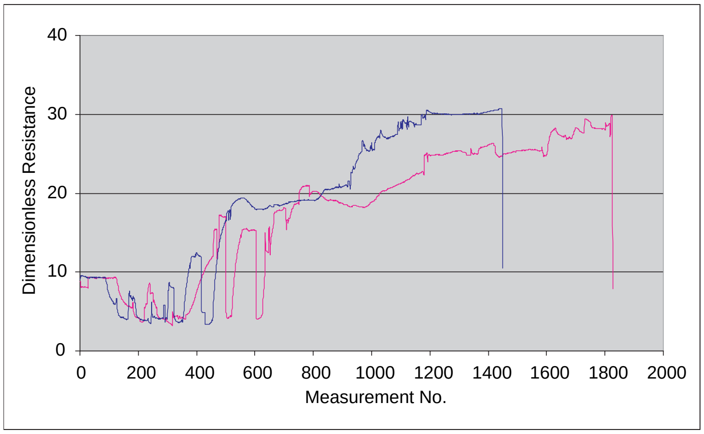


Figure 2. Mean resistance during filtration of 2 batches.

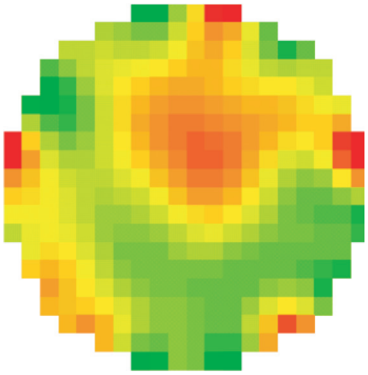


Figure 3. Tomographic image of slurry conductivity distribution.

regions within the filter, making the data sets amenable to statistical analysis.

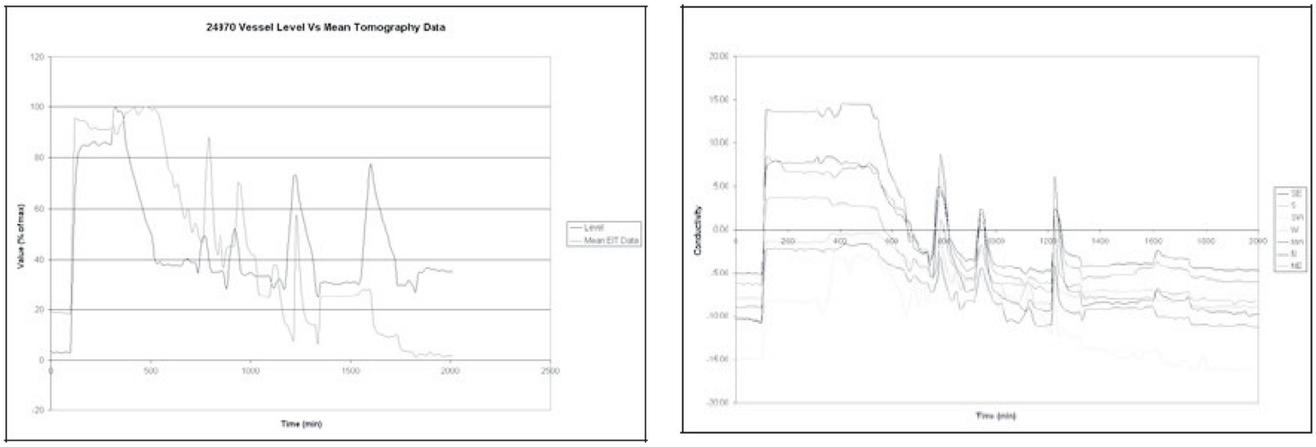
Currently these data are being collected continuously and, as a means of validation, it is being compared off-line with other process measurements and operator observations. The long-term aim is to use this information to improve fundamental understanding leading to minimization of product variability and improvement in product quality.

Figure 3 shows a tomographic image of the conductivity distribution through a section of the pressure filter. This demonstrates how one section of vessel (above the feed pipe) contains a higher moisture content cake (red being most conductive) at this time. This information can be used to inform the sampling strategy and, where necessary, as a means of reducing total drying time.

Grieve et al[8] discuss interpretation of the electrical measurements taken from the 36-m^3 pressure filtration vessel collected almost continually over a 4-month period. At this stage, image reconstruction techniques were not available for multiple electrodes mounted within the plane of the filter cloth. The 24 electrodes are arranged in 2 distorted rings of 8 and 16 electrodes within the plane of the filter cloth on top of the filter cloth hold-down bars. Initial interpretation of the data was conducted using statistical analysis of the electrical signals and relating these to the on-line measurements obtained elsewhere in the vessel. The most useful measurement for this purpose was the slurry level measurement provided by an acoustic reflection instrument. The mean conductivity trend for a single complete separation, washing, and drying cycle is shown and compared with the level trend in Figure 4A. It can be seen that although the mean conductivity signal is distinct from the level trend, a certain degree of validation of the mean conductivity signal is provided by the level trend. The overall trend in the mean conductivity is a decrease, because the slurry becomes a dry filter cake via a series of wash stages and a drying stage. The conductivity from 8 regions within the vessel is shown in Figure 4B by selecting 8 groupings of drive and receive electrodes across the filter cloth. These data indicate that the spatial conductivity distribution is not even throughout the filter cake, with the implication being that the filter cake solid packing or solvent composition is inhomogeneous. It is stated that additional laboratory-based experimentation is required to validate this potential inhomogeneity within the filtered cake.

Application of ERT to Stirred Tanks and Crystallizers

Williams et al[9] demonstrate the measurement of gas and solids distribution in a 30-L laboratory vessel equipped with 4 planes of ERT sensors (each consisting of 16 stainless steel electrodes on the circumference of the vessel and other additional electrodes mounted on the impeller shaft). Figure 5 shows a typical result from the gas dispersion measurements–the four cross-sectional conductivity maps have been stacked together and linearly interpolated between adjacent maps. A color scale has been used to



(A)

(B)

Figure 4. (A) mean conductivity and level measurement and (B) conductivity from 8 regions of the filter.[8]

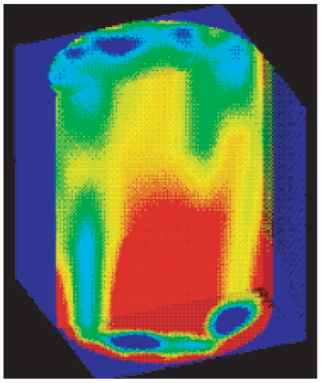


Figure 5. Conductivity maps for gas-liquid dispersion from a central sparger located at the bottom of a stirred tank.[9]

distinguish the conductivity, and, hence, gas hold-up variations within the volume. Red, yellow/green, and blue correspond with high, medium, and low gas hold-up.

A laboratory scale rig has been designed and built to evaluate the suitability of ERT for modeling and analysis of pharmaceutical mixing processes.[10] A vessel of nominal capacity 3.5 L was constructed from glass with a geometry designed to mimic pilot plant vessels and operating conditions. The jacketed vessel was fitted with 65 platinum electrodes (4 rings of 16 electrodes and an earth electrode) and provided operation over a wide range of temperatures, good optical access, good chemical compatibility, and minimal electrode protrusion. Data acquisition was by a P2000 ERT system by ITS. The reported work focused on mixing and progress of a chemical reaction.

The image reconstruction algorithm produces the electrical conductivity distribution on a 316-pixel circular grid. Because the vessel was fitted with 4 sensing planes, this results in the equivalent of 1,264 nonintrusive conductivity probes. The pixel data were used to determine t_{99}, which is the time to reach 99% homogeneity. In general the mixing-time measurements showed good reproducibility and followed the expected trend. The data obtained were compared with correlations from literature, and good agreement was found.

In addition to mixing times, Ricard et al[10] used ERT to monitor the hydrolysis of ethyl acetate to assess the suitability of the technology to monitor chemical processes. The change in electrical conductivity over time is proportional to conversion because of the consumption of sodium hydroxide and the large difference in mobility of OH^- and $CH_3CH_2^-$ ions. To compare the ERT data with that from another on-line measurement technique, a Raman probe was used to follow the reaction. The Raman spectra were analyzed by Iterative Target Transform Factor Analysis and are shown in Figure 6.

It can be seen that there is good agreement between the average bulk conductivity measured by the ERT system and the data obtained from the on-line spectroscopic measurements, and the authors conclude that this demonstrates the applicability of ERT to monitor the conversion of a dynamic chemical process.

Stanley et al[11] have demonstrated the application of ERT to a precipitation reaction in a pilot-scale vessel (2.3 m^3). The vessel was equipped with 8 planes of ERT sensors (each consisting of 16 stainless steel electrodes), which gives 8 × 316, or 2,528 pixels. The reaction under investigation was the semibatch precipitation of barium sulfate. The measurements are presented as time-wise conductivity

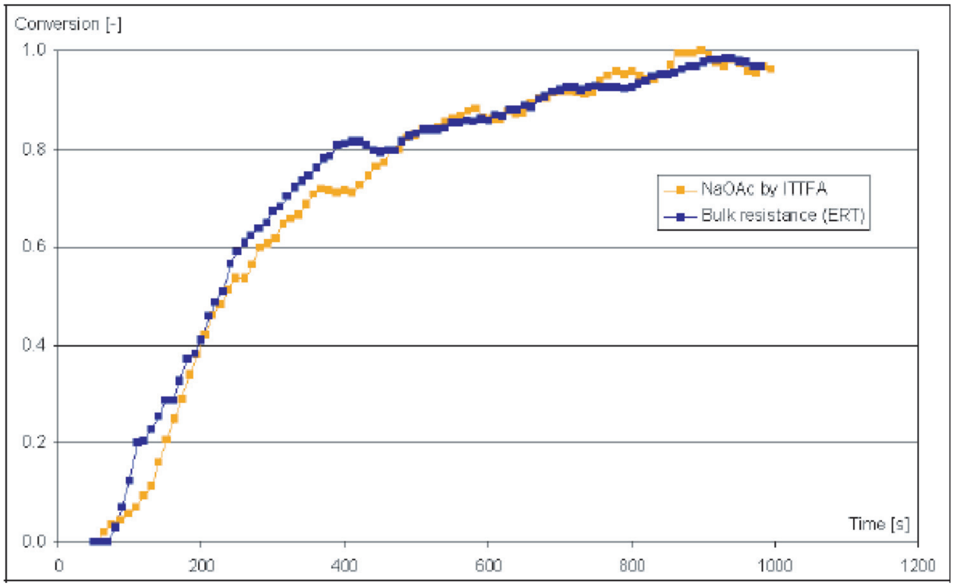


Figure 6. Variation of normalized concentration of sodium acetate over time measured using ERT and Iterative Target Transform Factor Analysis.[10]

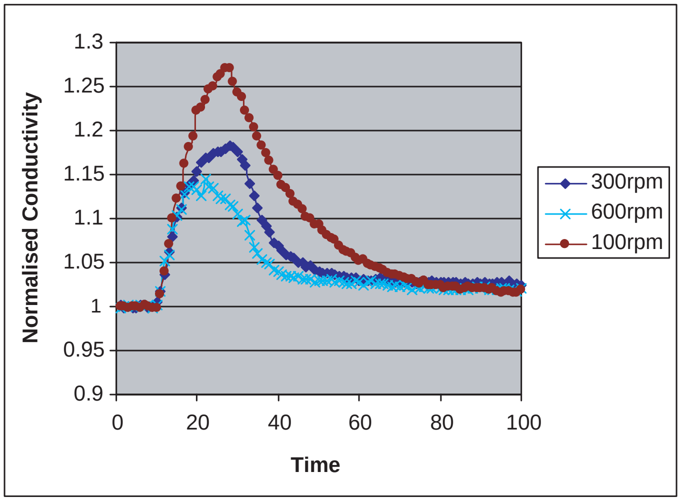


Figure 7. Bulk conductivity during barium chloride addition to sodium sulfate at different agitation rates.

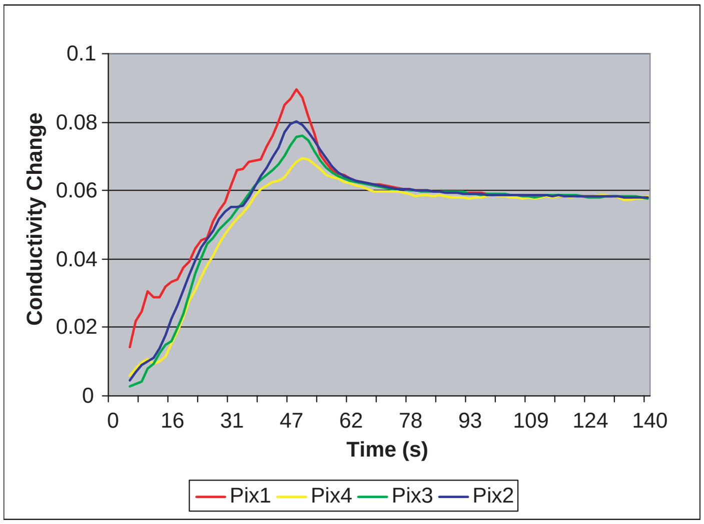


Figure 8. Conductivity for 4 pixels during precipitation of barium sulfate.

profiles showing the mean, 5th and 95th percentile pixel conductivities and 3-dimensional conductivity images. Measurements were collected for 2 feed addition times with and without agitation. There was a marked contrast in the results with and without agitation with the conductivity profiles displaying very different features. The 3-dimensional reconstructed images also displayed different features; in the case of the agitated system, the feed plume appears as a region of high conductivity, whereas in the case of the unagitated system, the reverse is observed—the feed plume appears as a region of low conductivity. The authors postulate that the region of high conductivity representing the feed plume in the agitated case is because of the presence of dissociated barium and chloride ions, which are unmixed and, therefore, unreacted. In the unagitated case, the authors suggest that the lack of agitation causes a high concentration of barium chloride at the feed addition point leading to immediate formation of precipitate. This causes an ion deficit around the feed point, giving rise to a low-conductivity plume. Barium chloride added after this will not come into contact with sodium sulfate for some time and relies on convective mixing induced by the feed to transport it to regions where sodium sulfate is present and primary nucleation can occur.

Recent work, performed at ITS, illustrates the differences in bulk and localized properties during a batch-precipitation process. Figure 7 shows the bulk conductivity when barium chloride is added to sodium sulfate for 3 agitation rates. The data follow the expected trend of a decrease in peak conductivity as agitation rate increases.

Tomographic measurement techniques provide spatial information from process vessels. Figure 8 shows the conductivity change during a twin-feed precipitation of barium sulfate for 4 pixels. The entire data set for this experiment consisted of 1,264 pixel values. This type of information can be used to optimize feed positions to minimize peak concentrations of reactants, which may cause unwanted byproduct formation.

ITS has started working with suppliers of glass process plant and glassed-lined steel process plant to develop ERT sensors for retrofitting to process plant. Bolton et al[12] report the development of a linear ERT sensor integral to a glass-lined steel cylindrical baffle fabricated by Pfaudler-Balfour to fit an AE630 pilot reactor at their Research and Development facilities in Leven, Scotland. The sensor had a length and diameter of 1,200 mm and 120 mm, respectively, and was fitted with 10 platinum electrodes. The sensor was used to measure the axial distribution of solids as a function of agitation rate within the reactor as shown in Figure 9.

This collaboration with process plant suppliers has continued, and Figure 10 shows a glass-lined beaver tail baffle and a small glass baffle, both integrated with a linear ERT

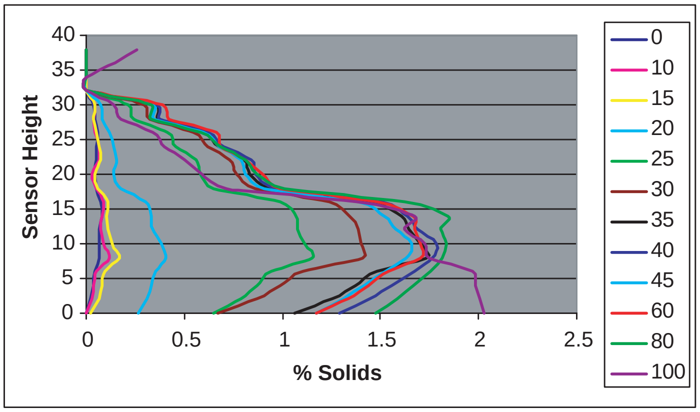


Figure 9. Axial solids distribution in an industrial reactor at a range of agitation speeds.[12]

Figure 10. Glass-lined steel beaver tail baffle and glass baffle fitted with linear tomography array.

array of electrodes. The beavertail baffle sensor has 16 platinum measurement electrodes and can replace an existing baffle, thereby not requiring an additional port on the vessel lid.

Pharmaceutical manufacturing companies are currently testing these sensors. Figure 11 shows a screen shot from the ITS software indicating the axial conductivity profile in a stirred tank containing a solid-liquid suspension. By suitable calibration, the axial solids profile may be determined from this conductivity profile.

Recent work has involved the use of a glass linear sensor to monitor the progress of crystallization of a pharmaceutical product from ethanol. Results were compared with measurements from a particle vision measurement system, and the ERT sensor clearly detected the onset and progress of crystallization. In a separate project, ITS has developed a system to monitor the status of a precipitation process in nitric acid, which is being tested in an industrial plant.

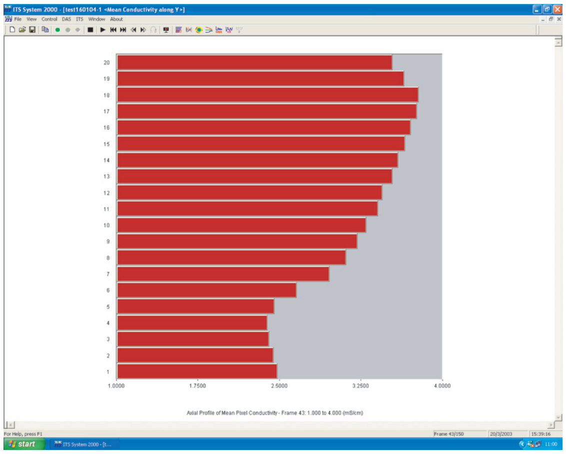


Figure 11. Axial conductivity profile within a stirred tank.

Application of ERT to Bubble Columns and Packed Beds

Wang et al[5] demonstrate the application of ERT to identify the flow regime and maximum interfacial area in a laboratory-scale bubble column. Features indicative of air concentration and bubble fluctuations have been extracted using mean conductivity and derivatives from a sequence of dynamic images. Furthermore, these parameters have been used with a close-loop Proportional Integral Derivative (PID) controller to maintain the flow with the maximum interfacial area in the bubble column using the bandwidth of bubble fluctuation.

Measurement of gas hold-up by ERT in a bubble column has been compared with those obtained by pressure transducers and an optical probe,[13] and good agreement was found. The ability of ERT to diagnose the functioning of the sparger in bubble columns was demonstrated by systematically plugging portions of the sparger.

Packed-bed reactors are used for a wide range of industrial processes. Radial flow packed beds offer a larger mean cross-sectional area and reduced distance of travel for flow compared with traditional vertical columns. Consequently, the pressure drop in these annular geometry reactors is reduced radically. However, it has been known for such geometries to introduce flow distribution problems given that pressure drops across the bed are sometimes of the same order as those in the distributor region.

Bolton et al[14] report on the application of ERT to qualitatively demonstrate the flow pattern through a radial flow-packed bed model reactor of novel design to confirm the design intent. Figure 12 shows a time series of tomographic images from a single measurement plane after the injection of a high-conductivity tracer in the inlet. The successive tomograms show the build-up of the tracer near the vessel wall, then the front moves toward the center of the reactor, and the trailing edge of the tracer detaches from the wall and moves toward the axial exit zone. Differentiation of the

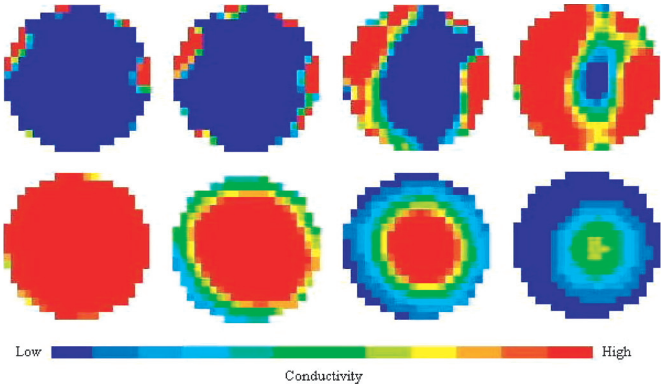


Figure 12. Time series of tomographic images from a single measurement plane after injection of high-conductivity tracer.[14]

numerical data making up the time series of tomographic images from each plane and, particularly, the location of the leading and trailing edges of the pulse was performed to yield flow maps and spatial velocity vector distribution. This information was used to validate computational flow dynamics calculations, which allowed increased confidence in the extrapolation of a model-based design technique when applied to the design of the full-scale reactor.

CONCLUSION

Electrical resistance tomography is becoming an established measurement technique for investigating the behavior of multiphase mixtures. In recent years, ITS has been working alongside process companies, including major pharmaceutical companies, to development the technology from a laboratory based technique to one that can be installed on process plant. This has included instrumentation developments to comply with the requirements of Intrinsic Safety certification for operation in flammable atmospheres; sensor developments in terms of electrode architecture and materials of construction to allow retrofitting to existing process vessels, operation within chemically aggressive environments, and compliance with Food and Drug Administration regulations; and development of bespoke software user interfaces to focus on specific measurement objectives.

These systems are providing information on the actual performance of manufacturing processes and insights into process dynamics that influence product quality and manufacturing performance. ERT and other process analytical measurement technologies can provide a fundamental understanding of these manufacturing processes.

REFERENCES

1. Williams RA, Beck MS. *Process tomography: principles, techniques and applications*. 7th ed. Oxford, UK: Butterworth-Heinemann; 1995.

2. Mann R, Dickin FJ, Wang M, et al. Application of electrical resistance tomography to interrogate mixing processes at plant scale. *Chem Eng Sci.* 1997;52:2087-2097.

3. Vlaev D, Wang M, Dyakowski T, Mann R, Grieve BD. Detecting filter cake pathologies in solid-liquid filtration: semi-tech scale demonstration using electrical resistance tomography. *Chem Eng J.* 2000;77:87-92.

4. Williams RA, Jia X, West RM, et al. Industrial monitoring of hydrocyclone operation using electrical resistance tomography. *Miner Eng.* 1999;12:1245-1252.

5. Wang M, Jia X, Williams RA. Electrical tomographic imaging for bubble column measurement and control. In: McCann H, Scott DM, eds. Proceedings of SPIE, Volume: 4188. Bellingham, WA: SPIE; 2001:114-121.

6. Grieve BD, Dyakowski T, Mann R, Wang M. Interfacing of EIT into an industrial pressure filter: a practical example. *Proceedings of the 1st World Congress on Industrial Process Tomography*, Buxton, UK, April 14-17, 1999.

7. Grieve BD, Smit Q, Mann R, York TA. The application of electrical resistance tomography to a large volume production pressure filter. *Proceedings of the 2nd World Congress on Industrial Process Tomography*, Hannover, Germany, August 29-31, 2001.

8. Grieve BD, Davidson JL, Mann R, Lionheart WRB, York T. Process compliant electrical impedance instrumentation for wide scale exploitation on industrial processes. *Proceedings of the 3rd World Congress on Industrial Process Tomography, Banff, Canada,* September 2-5, 2003.

9. Williams RA, Jia X, West RM, Roberts KJ. On line measurement of solids distributors in stirred tanks and crystallizers using electrical computed tomography. *International Conference on Mixing and Crystallisation.* April 22-25, 1998; Tioman Island, Malaysia.

10. Ricard F, Brechtelsbauer C, Lawrence C, Xu Y, Pannier A. Application of electrical resistance tomography to pharmaceutical processes. *Can J Chem Eng.* 2005;83(1):11-18.

11. Stanley SJ, Mann R, Primrose KM. Interrogation of a precipitation reaction by electrical resistance tomography. *Am Inst Chem Eng J.* 2005;51(2):607-614.

12. Bolton GT, Qiu CH, Wang M. A novel electrical tomography sensor for monitoring the phase distribution in industrial reactors. *Fluid Mixing VII*, July 10-11.

13. Fransolet E, Crine M, L'Homme G, Toye D, Marchot P. Analysis of electrical resistance tomography measurements obtained on a bubble column. *Measure Sci Technol.* 2001;12:1055-1060.

14. Bolton GT, Hooper CW, Mann R, Stitt EH. Flow distribution and velocity measurement in a radial flow fixed bed reactor using electrical resistance tomography. *Chem Eng Sci.* 2004;59:1989-1997.