Aber knowledge base

In conversation with **Dr Bob Todd**

Dr Aditya Bhat (VP Technology, Aber Instruments) and Dr Sven Ansorge (Director of Manufacturing, ExCellThera) had an in-depth conversation regarding capacitance technology, how it is perceived with respect to PAT, the importance of capacitance technology to be manufacturing ready and finally, how the technology can benefit the viral vector/ vaccine production processes. Dr Ansorge is an expert on capacitance measurement and on viral vector manufacturing processes. Hence, his perspective on the subject is unique and very much appreciated!
Here is an excerpt of their conversation.

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ABER

AB: Good morning, Bob, how are you doing?

BT: It's actually afternoon, here.

AB: So yes, just so everyone knows, I'm based in the US in Virginia, on the East coast. And Bob, obviously you can tell everyone where you're based.

BT: Yes, I'm in mid Wales, near the West coast of the UK.

AB: There you go. Yes.

So I just want to set the scene, Bob, for this conversation. And first of all, I'm really thankful and grateful that you've agreed to be a part of this.

ABER Instruments has been around for more than 30 years, now. And the technology that you guys invented back in 1988 has been functioning in so many of the big bio pharmaceutical companies, and all of the major breweries.

So I thought it would be a very good idea to just have a conversation with you to understand where the technology originated, initially, how the germ of the idea, if you will, originated.

And I think because so many people benefit from this technology today in our industry, I'm sure people would appreciate finding out a little more about the background of the technology.

So the main theme, I would think, of this conversation would be, invention of the technology, its implementation, and the challenges that you guys initially faced, which I'm sure would be quite significant and plenty.

And then, of course, we talk about the evolution of the technology and how the technology has evolved over the past 30 years and how it's perceived in the industry. And I can definitely speak a little bit about that myself.

Just to begin with, Bob, to give you give the listeners and viewers the context. I have had a very long standing relationship with you. In fact, when I first started working with ABER, you were the R&D director, and I was a research scientist in the R&D department.

And I've always been very grateful to our conversations. We've had conversations surrounding the technology multiple times. But I don't think we've officially sat down and spoken about how the technology was invented.

Q So if you were to initially just give us a background on you, what you were doing when the idea first came to you, that would be really interesting.

BT: Okay, well, my background is really in electronics. So biology was a bit of a shock, really, to me back in those days I used to teach electronics at university, and PhD in electronics, and I've worked on various projects over the years. And I was doing just that when a good friend of mine, Douglas Kell, came along and said -- I've got a little thing you might be interested in. I've had this our idea. And he said, going way back, many, many decades back, people have played around with measuring living matter, and discovered that it had some slightly strange electrical properties.

There are various papers scattered through the literature about it. And it was Doug's idea to use this, potentially as a way of actually measuring biomass in real time. And he I think it was the first person to actually suggest using that sort of measurement as a real time, useful measurement. Particularly interested in doing it in fermenters so that you had a pretty immediate measure of what was going on, rather than having to take samples and wait and so on.

Q Was this in 1988? Or I'm guessing it was...

BT: A couple of years before ABER instruments was actually set up. Yeah.

And he managed to persuade a friend of his in industry to give us a bit of money to explore the possibilities.

We did some initial work at the university, in Aberystwyth using a research student and a very expensive impedance instrument bought from Hewlett Packard at the time. And it started to look promising. So we realized that the technology for actually measuring this impedance was not really there at the moment.

We had this big, heavy box. The samples had to be in a little test cell right on the terminals in front of this box. And the whole thing drifted with temperature in a fairly alarming fashion.

But it did show that the idea was a going possibility.

So as I say, we've managed to get some money to explore it. And I spent probably a year or so trying to develop the initial, some electronics that would make it practical to use.

It clearly had to be something which was proof against environmental interference, which is temperature, all the electrical interference, which is, as you know, in an industrial situation, it can be quite severe. And it had to deal with measuring what's basically a very tiny capacitance in the face of a very high conductance.

I think Doug Kell wasn't quite honest about this in the early days, quite how difficult it was.

AB: For good reason.

BT: It may have been intentional on his part, so as not to say -- no, it's impossible.

The problem is that when you stick some electrodes in a typical medium, and you measure the current flowing, even when there's some cells in there, nearly all the current is just ionic current flow because of the salts dissolved in the liquid.

And gradually it turned out that the bet you were really looking for which was the capacitance, which is really just a question of measuring slightly-out-of-time current. That's a current which is slightly out of step, out of phase, with the voltage you apply.

So the conductive current is exactly in phase and in time with the voltage you're applying, and we were looking for this tiny bit. And it turned out that the bit we were looking for is probably something like 100,000 times smaller than the bulk current that you were measuring.

It gradually emerged that that was the target we were after.

So you certainly couldn't do that with the original instrument that we had. And the other problem was, we needed to have a probe that you could put in fermenters. And ideally, that probe needed to be on the end of a longish cable so that you could fit it to various fermenters and so on. You couldn't have these huge great box right alongside the fermenter or wherever you were trying to measure.

So that was a challenge as well. And the early instrument didn't attempt to pack the whole measuring system into what we now call the head amplifier, which is the bit that just goes on to the end of the probe.

What we had was cables carrying the radio frequency signals from the probe -- to and from the probe -- back to a big, heavy box which had quite a lot of large scale electronics in it at the time. And we managed to get that working.

Hit lots of problems along the way, as you can imagine. One or two quite funny ones. I'd been having trouble with the zero drifting. I had this beaker of saltwater on my bench with a probe in it, and the readings were gradually drifting. And Doug Kell came in one day, and taking one look at it and saying -- well, you've got algae growing in there. [laughs]

Yeah. Not being a biologist, really, just hadn't occurred to me that that was going to happen.

AB: But it's incredible, isn't it? Because even today when we talk about our technology, we say that it's so important to get the correct zero before you inoculate your cells

So I find it quite fascinating that so many years ago, even before the technology was officially invented, if you will, you were trying to first establish a stable zero. But of course you were... You were of course not aware that algae was growing on it.

So, in fact, the technology was working...

BT: Yes, exactly.

So we managed. I managed to understand that and did better later. And I have learned a bit about algae over the years.

But having sorted that, we still had some zero drift problems. And at first I thought it was the electronics, and we tried all sorts of things to avoid that. And it still persisted. And eventually we realized that the plastics we were using to support the metal electrodes actually do absorb quite a bit of water very gradually.

AB: Oh, right, okay.

BT: And so the permittivity, which is how much capacitance material exhibits, really, the permittivity of water is 78, typically. Whereas plastics are about three.

So if you've got a mounting system for your metal electrodes, which is on plastic, you get a certain background capacitance, which is based on this dielectric constant of three. But even if you absorb a tiny percentage of water, which is 78, it pushes that background capacitance up significantly, and it happens quite slowly. So you get this slow creep upwards, which we were finding at first.

Q How did you discover that this plastic was actually absorbing water so slowly?

BT: Well, after a lot of head scratching, we decided to dry it out for a couple of days and see where it went back to. And if you warm it up and leave it for quite a long time, it actually goes back.

AB: Interesting.

BT: So, now we use much more sophisticated materials, and you can get plastics which have an extremely low water absorption. Although you might get a little bit of that effect, I mean, most fermentations, the duration of most fermentations, it wouldn't be significant.

AB: So, what our listeners and viewers would be familiar with is the fortron that we now use to embed the electrodes. And that fortron is an industrial plastic which, like you say, is a lot better at addressing the challenges that you mentioned you mentioned earlier.

BT: Yeah. So that got us started, and we could make some reasonably good measurements. And we'd concentrated then on trying to improve the electronics, so that the crosstalk -- you probably a lot of you are familiar with the idea of crosstalk -- this means in our world, that large changes in conductivity, like when you make significant pH adjustments and things like that, will affect the conductivity. And ideally, that shouldn't affect the capacitance at all. And achieving that is not easy.

So that was the next kind of electronic challenge, to minimize that kind of crosstalk.

And of course, initially, as I said, we were working with quite long cables. And a few of the people who bought or borrowed instruments to test in the early days -- they wanted cables like 20 meters long -- and we were carrying radio frequency signals backwards and forwards down these cables. And the matching between the different signals on the cable needed to be very good, and we had to develop means, because when you bend a cable like that it changes the behavior of the cable slightly. So we had to develop system that was independent of that kind of thing.

So there are all sorts of minor difficulties like that. But they didn't feel minor at the time.

And then we had couple of people who are kind of industrial champions, if you like, or brave people to try it in the first place. We had a guy called Chris Bolton in from the brewing industry. And we had someone also from the biotech department in ICI, at the time. They were looking at new bio-produced products.

So that was a huge help. But of course, once you start putting systems in a proper industrial setting, then you hit a whole host of other problems.

AB: Right.

Q So I was wondering, Bob, when you were inventing the technology and you were working on all of this, in your mind were you visualizing the bio process industry to adopt it first? Or the brewing industry?

BT: Well, I think we probably weren't sure at the beginning. But one of the factors was that the brewing industry was relatively simple conceptually, because most brewers do more or less the same thing. And yeast is easy to access and is easy to handle. So most of our early work was done with yeast. And the other nice thing about brewing applications is they work at fairly low conductivities.

AB: Yes, of course.

BT: They're normally down at a few milliseimens per centimeter. So, in many ways, it was a much easier thing to tackle, initially.

They also tend to sterilize using caustic soda or something like that rather than using very high temperature.

AB: Right. That certainly would have been one challenge. Because it is so common for probes and sensors to be reused in the industry. And it exposes the entire system to extremes of temperature and pressure.

Q So how did you guys deal with that challenge initially?

BT: Well, once we started putting them in some biotech situations, it was apparent that it was a much more regime, really. And we did a lot of tests...

Q Could you just repeat that?

BT: Yeah. Once we started to some systems out in the biotech situation, it became clear that the sterilization processes were a lot more punishing. They were... Well, in the lab scale, things were ["autoclaved"][19:38] In the industrial scale, there was a lot of high temperature steam sterilization, and some people followed that very closely by jets of cold water to cool everything down.

AB: Yes.

BT: And that's not very kind to the probe, which has got metal and plastic. Because the expansion coefficients of plastic [20:00] are very different to the metal electrodes which are in it.

So although we got results, we found the probe life wasn't good in that situation. Whereas in the brewing situation, without too much effort, we could get reasonably long probe life.

So the most useful and easy thing to do in the brewery was just to measure the yeast slurry, as it was added at the beginning of a fermentation. Because traditionally that's done by you have yeast slurry stored in a tank and you assess its concentration, how much yeast you've got in there. And if you want to be really clever, you assess the live concentration. And then you work out how much you got to add for a given size of fermenter and pump in that volume.

So it involves the lab doing testing. And the problem... There were quite a few problems with it, because the brewing process carries a like 24 hour thing going on, and the lab is offer not available when needed, and things like that. And also the lab tests are often based on one sample from the yeast tank. And the yeast in the tanks is not homogeneous. So you can get some quite big errors by that. And the knock-on effects of that is that it can seriously affect the fermentation times.

So that seemed to be a key application. And that's the first one we went for in the brewing industry.

AB: I've obviously had the privilege of traveling with the technology around the globe and actually viewing how the different breweries use capacitance measurement. And it seems such a simple yet such an ingenious idea to just place the ABER probe in the pitching line with the yeast slurry, like you said. And combining it with the flow meter signal so that totalizes the live number of cells that goes into the fermenter. So the biotech counterpart of this would be inoculation, really. Quite simply, inoculation.

So you're placing the ABER probe in the pitching line to make sure that you get the same number of live yeast cells in a fermenter at time zero.

And that very clearly, and evidently contributes to consistency in fermentation performance, consistency in beer quality. In fact, we've had... Maybe you haven't seen the recent case studies? One from Meantime Brewing Company in London, and the other one in the US, the Summit Brewing Company. They discovered that using the ABER technology actually reduced the fermentation time by a day or two, which is massive.

So it's just a simple thing of measuring your cells and controlling the number of live yeast cells, has an exaggerated benefit to the process.

BT: Yes, yes, absolutely. And a quality improvement very often as well, because a lot of the big brewers are keen that their products should be consistent quality wherever it's made around the world. And that's quite hard to achieve.

AB: So you want your beer that's brewed by in the US, to taste the same in Europe and Asia. And you're right, it does contribute to consistency and quality as well. Yeah.

BT: We're just talking about live yeast. And that's one of the key things that we saw very early on with this technology well, we were expecting it from previous work but the way in which dead yeast doesn't really show up in our measurement.

And many of you probably understand the capacitance we're measuring is actually associated with the cell membrane surrounding the cell. And when cells die, the membrane usually becomes electrically leaky. And that effectively

forms a short circuit across the capacitance that we're... Little bits of capacitance that each cell contributes. So as the cells die the membranes become more leaky, the capacitance gradually disappears.

AB: Yes.

BT: And so that means that we can measure only live cells and ignore really dead cells.

But it also opens up other possibilities for measuring the effect of agents on the cell's membrane as well. So there's potential in drug testing and all that sort of thing, for example.

AB: Yes, yes, Absolutely.

Q **And the other aspect to this is, our probe emits, like you said, an electric field. That then is capable of detecting live cells because they act as capacitors.**

So there is one question that the technical team is often asked, the applications team, is whether that electric field is in any way detrimental to the viability of the cells.

And obviously our technology has been around for more than 30 years. What we typically say is that the electric field is just so infinitesimal that it doesn't really impact the viability of the cells, especially in suspension cultures, where each cell is exposed to this electric field for a fraction of a second.

But having said that, we have a lot of experience with fixed bed bioreactors, immobilized cells, for instance, our probes are routinely placed in the Pall icellis nano, and five hundreds, without any noticeable impact on cell health or viability.

So I was wondering if that was some of one of the question that you had to handle in the early days as well?

BT: Yes, we did. People were a bit worried about that.

But I personally didn't do a lot on it. But Doug Kell and his team at the university did do work on that. And as far as we know, the field strengths that we're talking about are very, very small compared to the sort of potentials which [35:00] will upset cellular processes.

So I think that the thing is, we tend to think of, oh, we're putting a hundred millivolts between our electrodes, for example.

But when you work out how much that is actually across an individual cell, because cell is so small compared to where the electrodes are, it actually turns out to be fairly negligible sort of field strength.

You can obviously damage cells by volt too high field strengths. And people do obviously use it. But you can fuse cells together and things like that.

AB: Yeah, absolutely.

Q **So, another thing that I wanted to talk about was... Of course, capacitance, we measure capacitance in picofarads per centimeter. Pico being to the power of minus twelve. So we're obviously measuring really tiny amounts of**

capacitance to measure those tiny cells.

The unit of picofarads per centimeter is not always... People are not always familiar, and they wouldn't always think of picofarads per centimeter to give them cell density or viable via volume.

It is a common practice to converge capacitance to a more familiar form of measurement, like it could be optical density, dry weight, or cells per milliliter, etc.

So I would like to get your perspective on how it was in the early days. Because I'm sure when you approached a brewery or a biotech company and said, well, we'll tell you what's your cell concentration in picofarads per centimeter, you're probably met with some surprise.

BT: Yes. Well, there was a lot of convincing to do like that, yes, when you come in with a completely new thing. And certainly then, it doesn't give quite the same answers is what people have done before.

That's a whole interesting area. In the early days, I did go round quite a lot to potential customers doing kind of party tricks to prove that the thing worked.

We had a beaker of yeast and I had one of our biomass monitors with a big meter on the front. And you would add some yeast and see that it went up. And then I would add some chalk dust and see that it didn't affect it at all. So that's just to show that it's not the same as an optical density meter, which would have reacted very strongly to that.

And then the third part, the party trick was to add some octanol to kill the cells. And then you see that slowly the capacitance measurement go down.

So that actually, we were able to do that in front of quite a few kind of lunchtime seminar groups in a number of companies. And that actually got people thinking -- yeah, maybe this has got some potential.

AB: Quite a good experiment, though, Bob. It's as good an experiment as any, because you're measuring cells when you add yeast, and when you add chalk, you're adding to the optical density. But capacitance doesn't... So it proves that it's insensitive to the presence of solid media particles...

BT: That's right, yes.

AB: And then you're adding octanol and... It's funny you mention octanol, because at Manchester, I worked with octanol too, to kill the cells on purpose. And the octanol has quite a, I want to say, beautiful affect on cell death. Because almost a sadistic way, if you will but octanol actually, it goes into the cell membrane and then expands the cell before the cell contents burst open.

So on capacitance, you'd actually see an increase

BT: Goes up a little first.

AB: A little bit. And then it falls as the cells die. That's quite interesting. That's really good. I wasn't aware of this party trick of yours.

BT: Yes. Yes, I used to do that. It was tricky taking octanol on the aircraft.

AB: [laughs]

BT: Anyway... Yes. But then once people got more

into the technology and started to believe it, it was then, well, how well does it correlate with cell counts or with the other methods of measuring?

Of course, it's measuring a different thing if you do the maths on it what the capacitance measurement roughly follows the volume fraction of cells.

Whereas when you're counting cells, you're not counting volume, you're counting the number of cells.

So obviously, if you take various samples of yeast, if their cells aren't all the same size, then you're going to get big departures from. And of course, the cell size often varies during a fermentation. So if you come up with a correlation with one sample of cells, it doesn't necessarily hold the same calibration factor throughout the whole process.

So that took a bit of getting over. And in fact when we were doing some work with one of the big brewers who wanted to measure in the fermenter rather than just pitching, we actually had to build in a correction for that, so that over there period of the fermentation it automatically put in a different calibration factor.

AB: That is interesting.

Like I said earlier as well, a lot of our customers still typically convert capacitance to cells per milliliter or any other offline form of measurement. And to get that calibration factor today is quite straightforward. It's either a single point calibration or a multiple point calibration.

There are companies like Biogen and Corteva that have understood the importance of just measuring raw capacitance the way it is without having to convert it to offline counts. And use real time raw capacitance profile to devise control strategies for, let's say, feeding their complex nutrients or optimizing the nutrient feed, troubleshooting the process.

So it's taken a long time, of course. Because if you were to think about it, capacitance is relatively new to the industry as compared to or even offline cell counts.

But an increasing number of people now in academia and industry are coming around to understanding what capacitance actually measures, and understanding that the calibration factor is simply a multiplication factor. So why not just work with raw capacitance?

BT: Yes, that's right.

AB: And that's been encouraging to see, how much benefit. It immediately brings to the table, you don't need to take samples anymore. And you can just work with the probe inserted in the bioreactor does its thing. And you can control the process effectively just on raw capacitance.

BT: Yeah, yeah.

And very often, it's very useful to have just a kind of capacitance profile, which you can use as a check that the fermentation is going to plan. You don't need to convert it to anything else. It's really just...

AB: It's a fingerprint. It's a fingerprint of the process. Yes.

BT: And the other thing that we found fairly early on was some of the early pharmaceutical applications, where that the other thing is very... It's very useful for spotting morphological changes and some processes where you want to take some action to change the environment of the cells for some reason, maybe to stimulate some production of something or other, deciding just when to do that.

It's the other use that we found early on. Some people saying -- this is perfect for this. Because you immediately see when the cells are ready for that.

AB: I'm actually quite pleased that you mentioned this right now, will jog my memory a little bit the entire discussion about viral vectors on vaccine production. Our technology has been used to...

So, typically just to backtrack a little bit viral vectors are produced either in the million cells, like HTK293, or viral cells, etc. or insect cells, like SF9 cells.

And the way it's done is the cells are grown for a period of time, and then they're infected by the virus. The virus introduces itself into the cells, it replicates, multiplies and copy, and then it sort of bursts the cell open and that's how you recover the product.

What you mentioned earlier is quite relevant here as well. Because when you infect the cells with the virus, there is a morphological change seen and the electrical properties of the cell membrane change as well. And you see a sharp increase in capacitance because of that, whereas the offline cell density stays constant.

So, in fact, our technology is used as an indicator for successful infection. And then of course, after that, it identifies peak infection point, and then identifies when the cells start dying, when the virus particles are released.

So it gives you a proper, complete, detailed picture of the process, and like you say, can identify these points and then devise control strategies around it.

BT: Yeah, yeah.

AB: That's really useful.

The other angle to this is, over the years, people have discovered the shortcomings of offline measurements. So the fact that you've got to open up your bioreactor to contamination risks. The offline count itself is variable. Inter-operator errors are quite well known in the industry.

So that is pushing people to trusting a more online real time form of measurement, like capacitance.

So it's quite fascinating for me to see where the technology started and where it is today.

BT: Well, over the years, we've had to respond to that. Because particularly, once you get involved in the pharmaceutical industry, the standards and requirements for reliability and everything, all go up.

Our more recent products, we're very careful with the calibration and the EMC, the fact that we meet all the regulations on materials, radio frequency interference, safety, everything else.

So that's become quite a significant part of the business is making sure that the quality of the product from all those different points of view is satisfactory.

AB: Obviously our systems are used to control processes that are manufacturing products that are millions of dollars worth, and just really useful and significant products that are ingested as well by humans. So the standard has to be really quite high.

And I'm glad you mentioned that as well, Bob. Because truly this is not an overnight success.

This conversation definitely brings that to light from where the technology started from you...

BT: Yes.

AB: Trying to get the stable zero, to identifying electrical interference and how to get rid of it. Thinking about... Well, you mentioned the plastic absorbing water.

I mean, these things today's users would not even think about. But the fact is that we've honed the technology over the years to where it is today.

BT: Yes. It's gone from very much a lab thing that you were lucky if you got any decent results at all, to being quite a reliable user device, which hopefully you don't need to worry about the technology and how it works.

AB: Yes. Yes, absolutely.

Q So I think we're at that point in the conversation, Bob, where we can maybe just quickly provide our thoughts on where the technology is going in the future, from more an applications point of view.

So right now, of course, as we mentioned, brewing is big, bio-pharma companies are using the ABER monitor to control their processes, monitor cell density, etc.

Where do you see the technology being used in the coming 5 years, 10 years, 15 years?

BT: Oh, well, yes.

Well, we're continuously adapting to changing fashions in the industry, if you like. I mean, people... We're obviously still work with big fermenters, but with a lot of emphasis on very small fermenters and single-use fermenters, and that type of thing. And we've had to adapt our equipment and probes and everything else to that.

And as many of you know, the actual equipment now has the whole measuring system in a very small -- we still call it the head amplifier. But it's a lot more than amplifier.

AB: Yes. Our users would be more familiar with the term Futura.

BT: Yes, Futura, yes.

But we started off calling it a head amp years ago. And the name stuck, certainly within the company.

AB: A lot of people still call it the head amplifier, Bob.

BT: Yes. Well, we now have this little thing that's literally a couple of inches long and smaller than a matchbox, and it has the whole of the measuring system in it, really.

AB: Sorry, Bob. I think you're referring to the Futura Pico, which is essentially the smallest...

BT: Yes. Smallest that we make at the moment. Yes. And it's much more appropriate for small fermenters.

AB: Yes.

BT: And the other aspect is working with very small samples. We did a little bit of that a long time ago, but it was a very niche thing, and we made a few special probes for measuring samples down to a milliliter and less. But people are now interested in going smaller than that, and certainly for medical applications and things like that. We're talking very, very small. So we've done some, and some other kind of online blood measurements and things like that over the years. We've had some various projects, but they haven't all come to a commercial endpoint. But...

AB: I would probably back that up as well. Because, again, I've been quite privileged to be traveling with the technology for so many years, and I can not only observe where the technology is going, but also in some ways dictate it. Because, you know, the front of house team at ABER, we come back and feed information into R&D, and that's how we develop our products on their own. We're always very focused on our customers and their requirements.

In the recent past, I can think about this entire cell and gene therapy sector booming, regenerative medicine as a whole. So we've done some incredible work, preliminary nonetheless, but incredible work with the some academic institutions and also in the industry to prove that our technology can be used with CAR T-cell therapy.

These are the instances where the cells are the product, and that is our specialty anyway measure cells.

So you need the critical quality attributes of the process to be measured and controlled quite quickly. And that's where the ABER probe comes in.

We've also done some very interesting work with the NC State University, here in the US who measure 3D tissues. And we've had a couple of very interesting publications applications around that subject as well.

And we collaborate with something called ARMI, which, if I remember correctly, is the Advanced Regenerative Manufacturing Institute.

Firstly, they work on bringing in industry and academia together.

And essentially why this was introduced was because -- if someone were to lose an organ, people who work for the Army, Military, etc., Defense Forces, there's a lot of research going on to come up with regenerative medicine for people like this.

BT: Yes.

AB: And the ABER technology comes in to identify the quality of these 3D tissues, the 3D constructs in real time.

So I believe that there's a lot of potential for our technology to work with cell and gene therapy and regenerative medicine, hopefully, over the next few years.

BT: Yeah.

I was thinking, the other are that we are still working on this frequency scanning.

Because we've got a fairly wide frequency coverage with the instruments, and we're often trying to push that both ways up and down. But the ways of analyzing that and trying to find more useful measurements from it, there's a lot of information hidden in that. And in order to access it requires quite a lot of mathematical processing of the measurements. But it also requires really good measurements.

AB: So true.

BT: Because unfortunately, the sort of spectrum we get out of the impedance scan is a very blurred one. It's a very smooth curve. And it doesn't look as if it's got any very obvious features on it. It's not like a spectrum, an optical spectrum, or something like where you have lots of nice little sharp spikes.

AB: Yes.

BT: But the thing is, it's a lot of information actually in there. But it's in the form of subtle changes to that impedance curve.

So in order to kind of de-convolute that and get useful information from it, you have to have very good initial measurements. So, and interfering things like electrode problems, and fouling, and gas bubbles, and things like that make it quite hard to get those perfect measurements. But it's something that we're still pursuing, and being able to get a direct measurement of cell size, for example, would be a nice variable that, if you could reliably get that in some situations, we can already do that, but not in every situation.

AB: Yes.

BT: So we're trying to widen the ability to do that sort of thing.

AB: I can certainly provide some perspective on that as well. Because just to initially say that most of our customers utilize capacitance and conductivity measurements at a single frequency, or let's say two frequencies, and plot that against time to get the broad profile of the culture and that works quite well for all of the applications that we mentioned earlier.

But of course, what you're mentioning is measuring capacitance at different frequencies. And we do 25 frequencies right now in the radio frequency spectrum. And that frequency spectrum has a lot of hidden useful information about the cell culture.

And I can again tell you, that an increasing number of our customers are now interested in frequency scanning.

So quite interestingly, Biogen published a paper last year where they utilized FC, which is a critical frequency of the frequency spectrum, to identify apoptosis and culture much earlier, and they could reverse apoptosis just on the basis of that real time information, which was quite fascinating.

Other groups have utilized frequency scans to estimate like you said, cell size. Some work has been done to even estimate a percentage viability. So there's been a lot of work going on in the background. You're absolutely right. I do see frequency scans being used more and more over the next 5 to 10 years to extract so much more useful information.

BT: Yeah.

AB: That's certainly something that I am looking forward to supporting. Yeah.

BT: Yes. And I suppose the other completely different aspect is the single use, and very cheap, where you want to be able to throw the thing away, and you want it small, so that you can use lots of channels in parallel and things like that.

So that whole adapting to that new way of thinking, rather than reusable. Probes that supposed to last for years in glass fermenters and everything, it's a whole shift, isn't it, to plastic bags and mini-fermenters, and even working in micro-well plates, and things like that.

AB: Yes. Absolutely.

And of course, because of the applications that we mentioned earlier, cell and gene therapy applications, these are so, almost, frightened of contamination issues that, you know, you want to work with the technology that has experience of being installed in both reusable and single use bioreactors, and that's where it's going to be headed, really.

So, yeah, I completely agree with you.

Going smaller, going single use, and utilizing it for applications to test cell and gene therapy, regenerative medicines, you need to show that etc that its going to be the next big thing, along with, we mentioned measuring blood samples,

maybe...
BT: Yeah.

AB: And who knows what's out there? But it's certainly a very interesting time for this technology.

BT: Yes.

AB: I think, Bob, this is a good time for us to stop the conversation. Although I can keep talking to you about the technology for days on end.

Just to quickly sort of finish off the conversation here, Bob. Like I said much earlier on in the conversation, I've had a long standing relationship with you. I used to get a lot more opportunity to talk to you when I was there in ABER for so many years. But I miss that opportunity now. So I really cherish this conversation that we've had today.

I can also tell the listeners and viewers that you're an innately modest and humble man. So initially, you said that you didn't do anything about biology. But I can tell you today, and in fact, even when I started working for ABER Instruments, I've met very few people with such a level of expertise in both engineering and the biology side of things. And you're certainly one of them.

I know you always undersell yourself, but you've been such an integral part of the ABER journey and the technology that you guys invented back in 1986, 7, 8, is now being used for such important processes. And it's doing such a lot of good.

So, you really should be very proud of yourself, really. Thank you so much, Bob.

BT: Great. Thank you very much.

It's been a thrilling journey. And I think we've got a really good company out of it, too. It's a good place to work.

AB: Absolutely it is. Thank you so much, Bob.

Alright.

BT: Great. Bye.

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