A COOL BIOREPOSITORY

Large -80 °C storage compartments each containing up to one million samples are arrayed either side of an aisle robot, capable of retrieving over 2,000 samples a day © Justin Owen

Biobanking promises huge medical benefits by storing vast libraries of individual tissue samples and biofluids for research. The Automation Partnership (TAP) was one of four finalists in this year's MacRobert Award with their automated repository capable of safely storing millions of biological samples at the required temperature of -80 °C while allowing random on-demand robotic access. Justin Owen, Systems Architect for TAP, explains how this facility overcame the formidable challenges involved.

The UK Biobank is a pioneering project, whose mission is to collect and store 10 million small samples of human blood and urine from 500,000 different people for as long as 25 years – a vast resource that gives scientists an unprecedented opportunity to discover root causes of diseases.

Each sample in the Biobank is uniquely identified and can be linked to its donor. When a donor contracts a serious condition such as cancer, heart disease, or diabetes, their sample can be compared with samples of others who have developed the same condition and those who have not. By combining this data with medical histories of donors, analysts are confident they will make major progress in identifying key genetic and situational factors in disease.

Before scientists can put this world-leading effort into practice, however, engineers have needed to create a unique facility. For the initiative to be effective, the ultra-low temperature home of UK Biobank (named POLAR) will need to operate continuously with a core temperature of -80 °C using robots that can quickly, reliably and accurately store and retrieve samples 24 hours a day throughout the 25-year lifespan of the programme – without relying on human intervention. It is essential that the composition of samples remains totally stable at -80 °C, because if the cooling system fails and samples are allowed to thaw, they quickly become unusable, thus rendering the entire programme void.

BESPOKE SYSTEM NEEDED

These basic requirements of this novel and far-reaching initiative posed a wide range of challenges to our team at The Automation Partnership, or TAP. Not least of these is the fact that UK Biobank is a repository on an unprecedented scale. No one has created anything of this size before so we had no off-the-shelf engineering solutions to solve the problems. Most hardware had to be custom-made, not least robots robust enough to store or pick up as many as 2,000 samples each day; in an extremely hostile -80 °C environment. For a quarter of a century.

Our previous experience in creating high-integrity automated storage and retrieval systems for the pharmaceutical industry gave us the expertise and confidence that we could tackle this hugely complex enterprise successfully. Our team also had the benefit of experience in designing and building robotic systems for use in cold conditions, down to -20 °C.

POLAR installed at the UK Biobank. With a footprint of over 160m² and capacity to store over 30 tonnes of material, POLAR combines novel refrigeration, precision robotics and robust software technologies
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ENGINEERING COOL

Cooling for POLAR is provided by liquid nitrogen in a closed-loop system, the largest and most advanced of its kind in the world. This system is self-pressurised and self-pumping and was deemed far more reliable than conventional mechanical refrigeration (and cheaper in terms of capital costs).

The box-within-a-box design provides a very high-integrity cold-room that prevents the ingress of the big enemy in this business – moisture. The outer 'box' is constantly being purged with air that has a moisture content of just two parts per million. This retards icing, which if it were to build up could degrade the refrigeration process and endanger the long-term integrity of the bank and all its samples. Moisture also causes frost, which if it were to develop on the drawers would prevent the robot from reading the bar-codes on the sample racks – a basic but very real challenge that was essential to address.

Two 50,000-litre tanks feed liquid nitrogen through dual-redundant pipework to evaporators mounted inside the outer box in a way that ensures any ice that may ultimately build up at this coldest point of the system can be easily removed (ice this dry has the consistency of icing sugar). Similarly, all other routine-maintenance items are fitted externally.

The store operates in two modes, the core inner box running at -80 °C surrounded by an air gap within the confines of the outer box, with its -20 °C temperature. This is manned by two robots, one of which receives and hands back samples to the outside world (through an air-lock to an ante-room of the outer chamber) and trundles rapidly back and forth between the two facing tiled-wall cabinets, inserting and withdrawing racks of samples into and from the right drawers. Its workmate cherry picks individual samples from racks on request for delivery to researchers.

Using liquid nitrogen to cool makes the system intrinsically reliable. It means there is no compromise on sample storage temperature, -80 °C is easily achievable. There is negligible power consumption and no waste heat. The system is almost silent in operation and no nitrogen is vented into the store; the waste gas is directed out of the building
© The Automation Partnership

KEEP IT SIMPLE

UK Biobank, based in Stockport as a host project of the University of Manchester, invited us to tender for the project in 2004. We responded with proposals within three weeks and were nominated as the preferred vendor. One key priority we pursued right from the start was to minimise the number of moving parts, particularly in the refrigeration system. This system is designed to provide consistent and continuous performance for 25 years so simplicity and reliability are essential.

This is why we opted to break with convention and discard the only method of refrigeration currently in widespread use in large-scale, low-temperature storage systems: mechanical refrigeration. Conventional single-compressor refrigeration systems typically can only achieve temperatures of about -40 °C. To produce lower temperatures, a two-stage cascade refrigeration system is required, requiring two different refrigerants.

To keep an archive of this size at -80 °C would require driving the efficiency of a two-stage cascade refrigeration system very close to its limit. To sharpen the risk further, its associated complexity, plus its narrow margin for loss of performance, would impose a very high cost of in-service maintenance, with the need for specialist servicing and repair (often using proprietary knowledge) that may not be available for the next 25 years.

LN2

Instead, TAP and UK Biobank explored the viability of using liquid nitrogen as a refrigerant and elected to opt for this approach. Liquid nitrogen is injected into heat exchangers in the sample storage chambers and delivers powerful advantages over mechanical refrigeration. Our target storage temperature could be reached easily (liquid nitrogen boils at -196 °C) and we would benefit from fast cool-down and recovery rates, effectively giving unlimited cooling capacity.

Nitrogen gas pressurises the storage tanks, causing the liquid to flow when a valve is opened. Excess pressure is relieved by a pressure relief valve fitted to the tank. There is a great simplicity of design, with no highly stressed components and very few moving parts – in fact, no moving parts or serviceable items at all in the crucial ultra-low temperature cabinets containing the precious samples. Liquid nitrogen also provides clear benefits in terms of efficiency, absence of waste heat, quietness of operation and cost of ownership.

These advantages appeared compelling – but nothing on this scale had been attempted before. So we undertook

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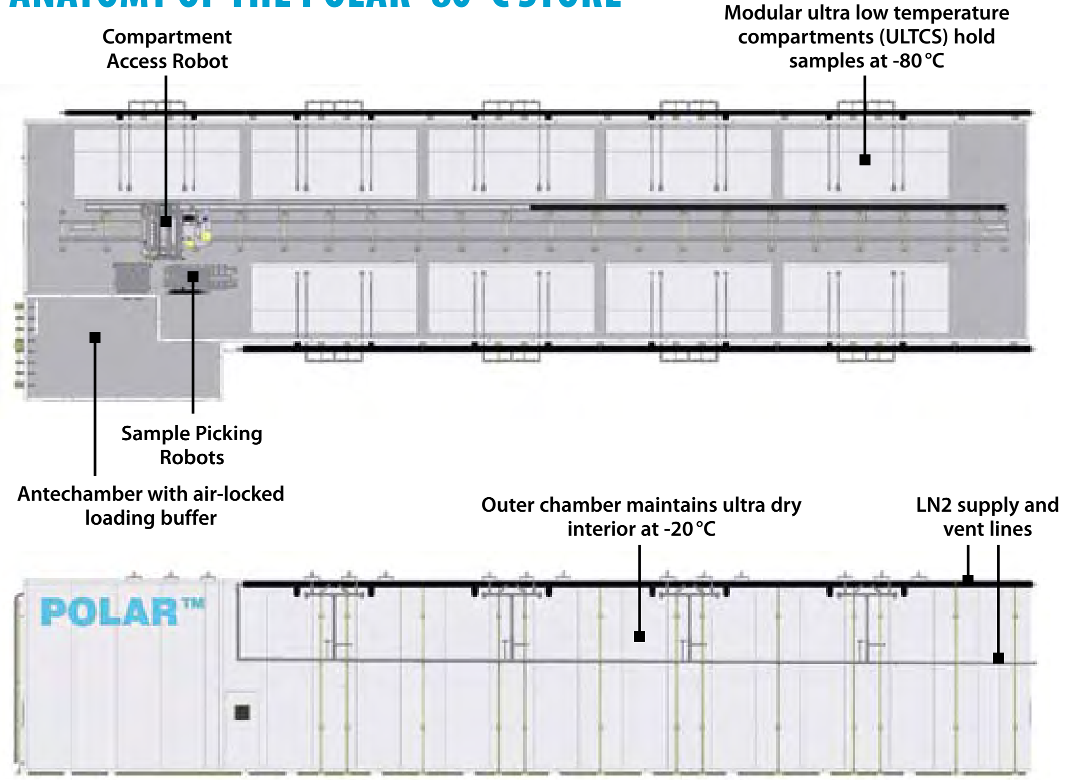
ANATOMY OF THE POLAR -80 °C STORE



an extremely thorough development and testing process before progressing with the full-scale storage system.

MAINTAINING COOL

Our approach exploits the advantages of a 'box-within-a-box' in which the inner containers for the samples are super-chilled to -80 °C, each has a wall of insulated storage drawers that hold the samples, like massive floor-to-ceiling, shallow-drawer filing cabinets. This design avoids the big drawback of a conventional refrigerator – the inevitable warming that occurs when samples are accessed by opening a large door.

In our design, the ultra-low temperature (ULT) compartments – the shallow drawers – are separated from a highly de-humidified -20 °C zone within the outer box by fixed insulated panels on all their surfaces. These tiled walls of storage-trays are accessible to a robot travelling along the access aisle and form seals effective enough to allow the refrigeration system to maintain -80°C conditions comfortably.

SMALL SCALE

Initial trial tests proved that only the samples held in the opened drawer experienced any change of temperature – even during a simulated failure when a drawer was left open indefinitely. At all times, the samples in adjacent drawers remained at -80 °C. When a drawer was opened for a realistic placement or retrieval time – typically 30 seconds – a single isolated sample tube was found to only increase in temperature to -65 °C. This is the worst case because fully populated storage racks gain warmth even more slowly because of their greater thermal mass.

Racks of samples are stored on shallow insulated drawers. Drawers are accessed and racks are picked and placed robotically

ROBOTIC RELIABILITY

Why design a system of this enormous potential value to medical science and make it rely on unthinking robots? Why not use humans to do the storage and retrieval of samples?

Human fallibility is the main answer. Observed trials of people running mass-storage and retrieval systems have shown error rates can reach as high as 10% of the total. Such unreliability would negate any statistical value of research undertaken. Not only that, but working in a -20 °C environment and identifying and opening drawers containing samples at -80 °C would endanger the health of the human as well as jeopardise the integrity of the sample.

Using robust robots, in fact, ensures the system can operate with 100% accuracy, complete reliability and at the rapid rate of some 2,000 storage and retrieval actions each day, points out Frank Tully of TAP, who developed POLAR's robotics.

Robust simplicity has been as important as functionality at every stage of the development work. James Pilgrim, who led the software development for POLAR, explains. "UK Biobank can be run with just one human operative loading and unloading batches of samples through the air-lock hatchway in the ante-room to the outer chamber. We designed this interface between robots and humans to be as simple as possible, effectively a staging-post with just a touch-screen and keyboard in the ante-room. Our software controls the computers on which the robot systems depend."

GIVING SAMPLES

Dr Tim Peakman, Executive Director of UK Biobank, says the blood and urine samples will empower a "prospective" research study, one of the largest of its kind ever undertaken. Up to 20 samples will be taken from each of 500,000 volunteers aged between 40 and 69, essentially a random selection of that age group from across the UK population. During this build-up phase of up to three years, POLAR will be busy stocking up with samples as people are recruited to the project at a peak rate of 700 a day. Then for the remaining 22 years or so of the programme, POLAR's robots will work mainly on retrieving samples required by scientists.

"When people among this group develop diseases in the next 25 years, researchers can use their samples in UK Biobank to determine the possible factors behind their illness, using the power of quantity to repeat and reinforce the accuracy and validity of their findings," explains Dr Peakman. "POLAR enables a more systematic approach to finding out why some people get diseases and others don't. The whole system has been designed to be capable of supporting research techniques for 25 years into the future."

As with blood donation, UK Biobank is not intended to help directly those who take part – but it should give future generations a much better chance of living their lives free of diseases that disable and kill.

Biobank samples are physically protected and can only be sourced by an authorised user. Operators are not exposed to ultra-low temperatures and work in a conditioned antechamber. The loading and unloading is safe and ergonomic and incoming samples are held at -20 °C while awaiting transfer to storage © The Automatin Partnership

Another factor underpinning the integrity of POLAR's design is the fact that less than 0.2% of the contents of the ULT cabinets are open to the -20 °C aisle temperature at any one time while archiving or accessing samples, limiting the number of samples exposed and preventing warming of adjacent drawers.

Having proved the soundness of this innovative approach, our team scaled-up the system to achieve the required capacity of 10 million samples. All samples are stored in individual 1ml sample tubes and mounted on standard laboratory racks that are handled robotically from initial storage to eventual retrieval. Overall, the UK Biobank facility signifies a civil engineering project in its scale – it is a massive storage system holding 30 tonnes of samples and labware. Yet this archive is also a high-precision engineering project in the way it required the implementation of totally dependable and accurate robotic systems.

In the impressive shape of the UK Biobank, medical science is about to gain an enormous and innovative asset that can exploit the benefits of scale to energise research into the root causes of disease. As engineers, my colleagues at TAP and I are as privileged to be associated with it as we are dedicated to ensuring its success.

The author would like to thank John Hutchinson for his help on this article.

BIOGRAPHY – Justin Owen

Justin Owen leads the Hardware Engineering Group at The Automation Partnership (TAP), Cambridge. In addition to managing his group he is still a practicing engineer, leading large development projects and providing engineering leadership for TAP's emerging portfolio of bench-top products. Justin's involvement with the UK Biobank began in 2004 when TAP was invited to tender for the -80 °C storage component of the project. He led the technology development and engineering from concept to end product and has recently taken the system through commissioning and successful site acceptance tests.

Further reference

www.ukbiobank.ac.uk

More about convection cooling can be found at www.automationpartnership.com