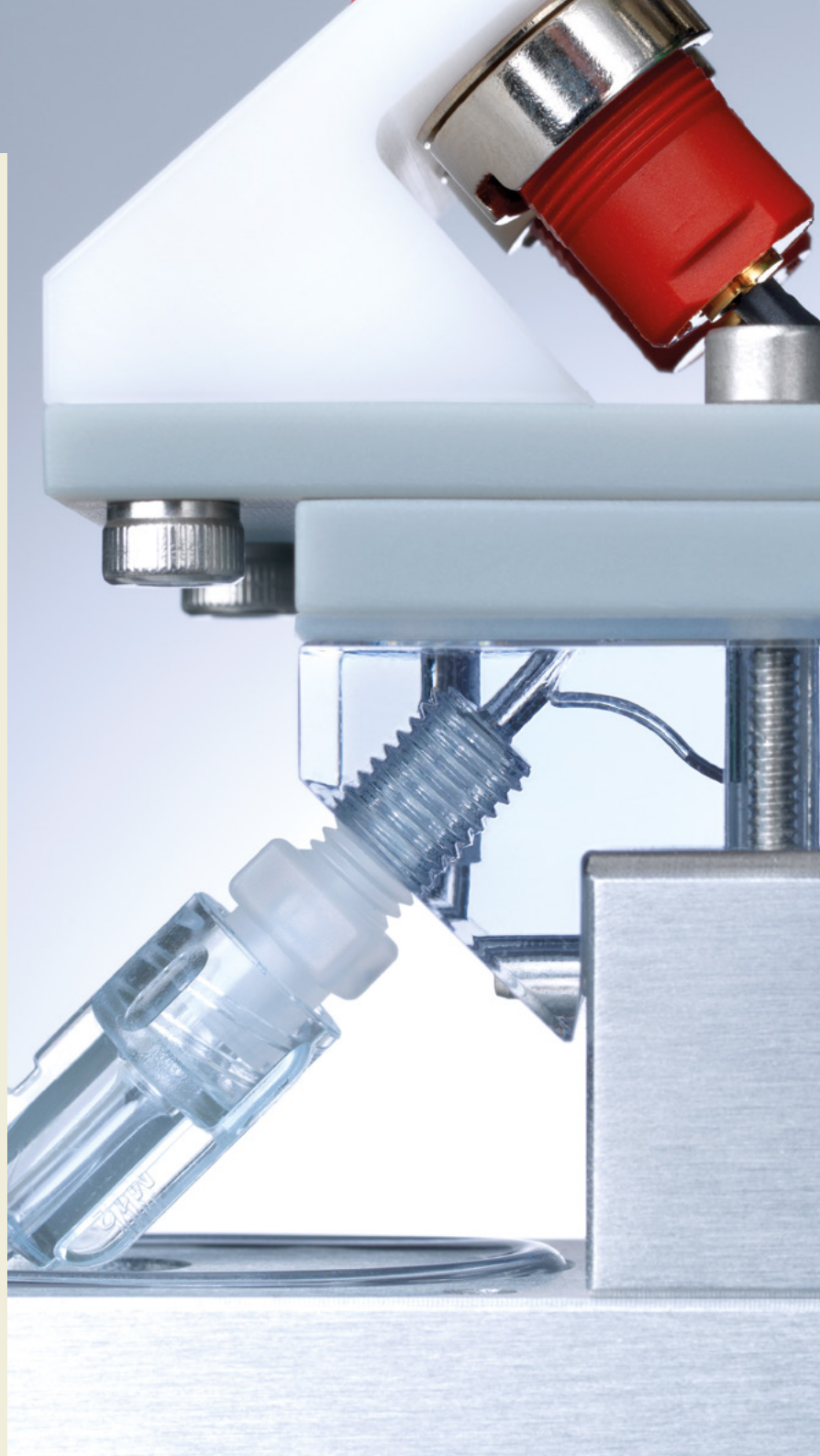
Automated biosensor testing for the development of continuous health monitors

For the nearly one in ten adults worldwide living with diabetes,[1] continuous glucose monitoring (CGM) can be life changing.

This is because real-time insight into blood glucose levels without the need for fingerstick tests greatly improves awareness, engagement and glycaemic control; reduces the mental burden of managing the disease; and enables automated insulin delivery (AID). In a recent study reported in the American Diabetes Association 2024 Scientific Sessions, the number of diabetes-related events leading to hospitalisation more than halved 6-12 months after type 2 diabetes patients on insulin therapy commenced CGM.[2]

Now the race is on to develop the next generation of CGM sensors. New sensor technologies promise patients greater convenience, for example through long-term implantation and even non-invasive glucose sensing, alongside other benefits such as lower cost and environmental impact, shorter start-up and response times, improved accuracy and ease of use, and detection of additional analytes.



The importance of test capability to build confidence in commercial CGM sensors

However, before a novel sensor can progress into clinical trials, rigorous testing is required to assess sensor reliability and accuracy across diverse physiological conditions. This is set out in the reporting requirements for integrated continuous glucose monitoring systems (FDA 21CFR862.1355).

As a result, in *vitro lab* testing plays a pivotal role in CGM sensor development. Sensors are subjected to a battery of experiments simulating various glucose concentrations and interferences.

But to support the rapid commercialisation of a novel CGM sensor, it is important to bear in mind that the challenge is not to demonstrate working prototypes, which may be feasible with manual testing and low-cost lab equipment. Instead, the challenge is to demonstrate that many 1000s to millions of manufactured devices will work reliably – depending on whether the sensor is an implantable or a short term wearable CGM.

Another way to highlight the challenge of sensor testing is to anticipate the sheer volume of data generated during a CGM sensor testing campaign. Over the course of several weeks, a single CGM sensor can generate hundreds of thousands of data points, and a sensor development programme could involve 10s of people testing many thousands of CGMs over multiple years.

The upshot is that CGM sensor testing is a major development activity. It takes considerable up-front time and effort to establish the test and data management systems to achieve this. And yet, time establishing test capability is time not spent on developing your innovative sensor.

Nevertheless, the reality is that you will need both.

Test Protocols

At TTP, we support clients in a wide range of development testing, from drug delivery devices to lab diagnostics.

In our view, it is always best to establish the testing capability as soon as possible in the development process. That way, the same reliable test protocols can be used throughout: first, to understand the effects of design changes and to select the best designs; then, to guide the refinement of the manufacturing processes; and ultimately to maintain confidence as the development progresses towards a product that will be manufactured, and will need to work reliably, in the 1000s or millions.

In fact, test systems that provide reliable, secure and accessible data can accelerate the whole development process by enabling rapid evidence-based investigation, troubleshooting and design decision making, and supporting regulatory approvals, so that new biosensors can benefit patients sooner.

TTP's Automated Sensor Testing Platform

We have created an automated CGM sensor testing platform to support your technology development and bring a new CGM solution to market without hold-ups.

The platform supports high-throughput, automated and parallel sensor testing for extended periods of time. The core testing hardware has been designed to meet the specific requirements of CGM sensor testing.

Together with data capture, storage and analytics, it provides a platform for developing and demonstrating the performance of your technology.

At the same time as addressing all the needs of a typical CGM sensor testing campaign, TTP's platform has been designed to maintain flexibility and allows for rapid customisation as needed.

Automated fluidics

At its core, CGM sensor testing means running a large number of fluidic experiments during which sensors are exposed to varying glucose concentrations in order to demonstrate responsiveness and long-term measurement stability.

To take the place of painstaking manual experiments, we have developed a robust automated fluidics platform capable of running repeatable test sequences with expandable numbers of test fluids and sensors, with UV sterilisation and filtration provided to control microbial growth in longer term tests.

For long-term sensor testing, the system can switch automatically between through-flow, for calibration checks with rapid concentration changes, and recirculation, flowing a fixed concentration test fluid past the sensor to assess long-term drift.

Our system (see Figure 1 on next page) also offers additional elements for controlling and maintaining the conditions under which sensor performance is assessed.

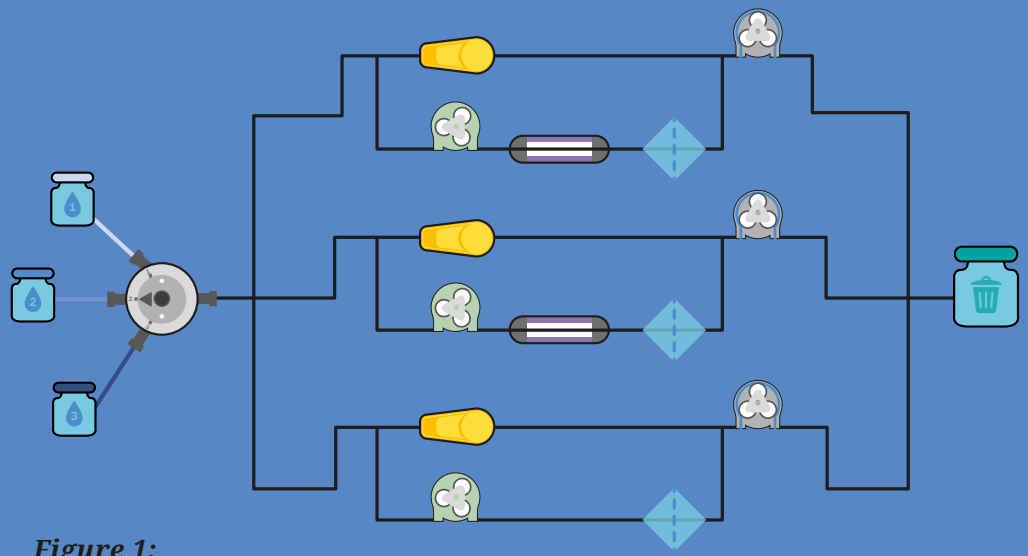
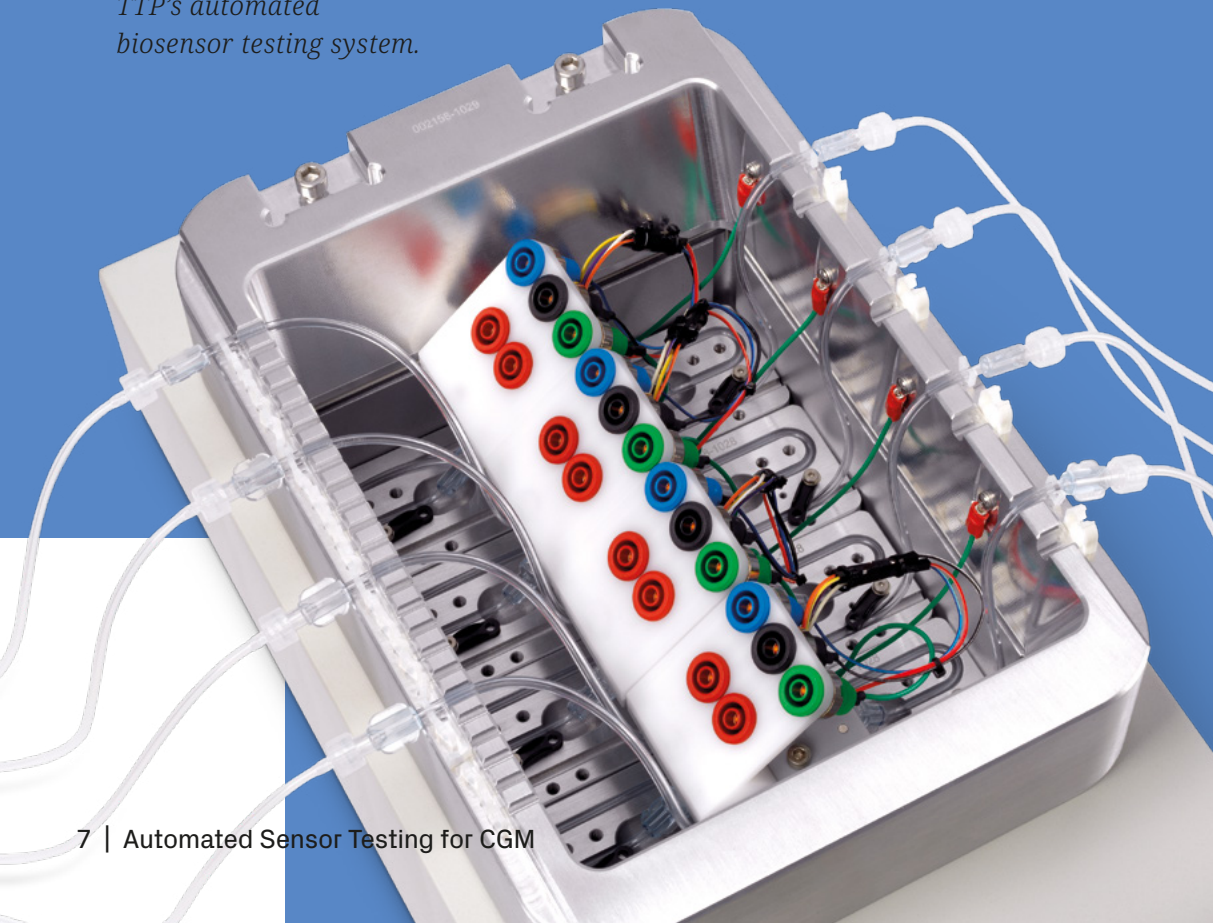


Figure 1:
TTP's automated biosensor testing system.



Temperature control

The system uses a dry block heater to regulate the temperature of tubing and flow cells. Temperature control is critical to measure performance shifts with temperature, or to hold the temperature constant when other factors are the focus.

Sterilisation

During long-term testing, sterilisation is needed as microbial growth in PBS/glucose solutions at 37^{0}C could consume glucose and damage the sensor. The system is equipped with a steriliser using UV LEDs to deliver a typical 90% kill dose of 100J/m^2 in a few seconds.

Oxygen sensitivity

Oxygen monitoring and control functions can be added when investigating oxygen sensitivity, as oxygen levels can strongly influence the performance of glucose oxidase and fluorescence-based sensors.

Flow cell designed for glucose sensor testing

The core part of the fluidic system for sensor testing is the flow cell, in which the CGM sensor is exposed to pre-defined sequences of glucose and other test solutions.

What are the particular requirements for CGM sensor testing?

- Glucose concentrations need to be changed rapidly to reveal the sensor response time (rather than the speed of the fluidics or filling and flushing of the flow cell).
- Low flow speeds are needed to minimise convection effects and forces on flexible sensor structures.
- Glucose must be held at a series of fixed concentrations to generate calibration curves.
- When testing many sensors in parallel for long periods of time, it is helpful to minimise the volumes of fluids used.

What makes our flow cell different?

TTP's flow cell has been designed with a smooth profile to avoid dead volumes. This allows the concentration to stabilise to within 1% in a few seconds with a pumped volume of less than 40 microlitres. Although the volume has been minimised, the flow cell fits a wide range of CGM sensor filaments.

In our CGM sensor testing platform, flow cells are connected in parallel rather than in series to test multiple sensors. While this requires more complex fluidics, it has the key advantage that concentration steps are synchronised and identical in every flow cell, allowing the most direct comparison between all the sensors under test.

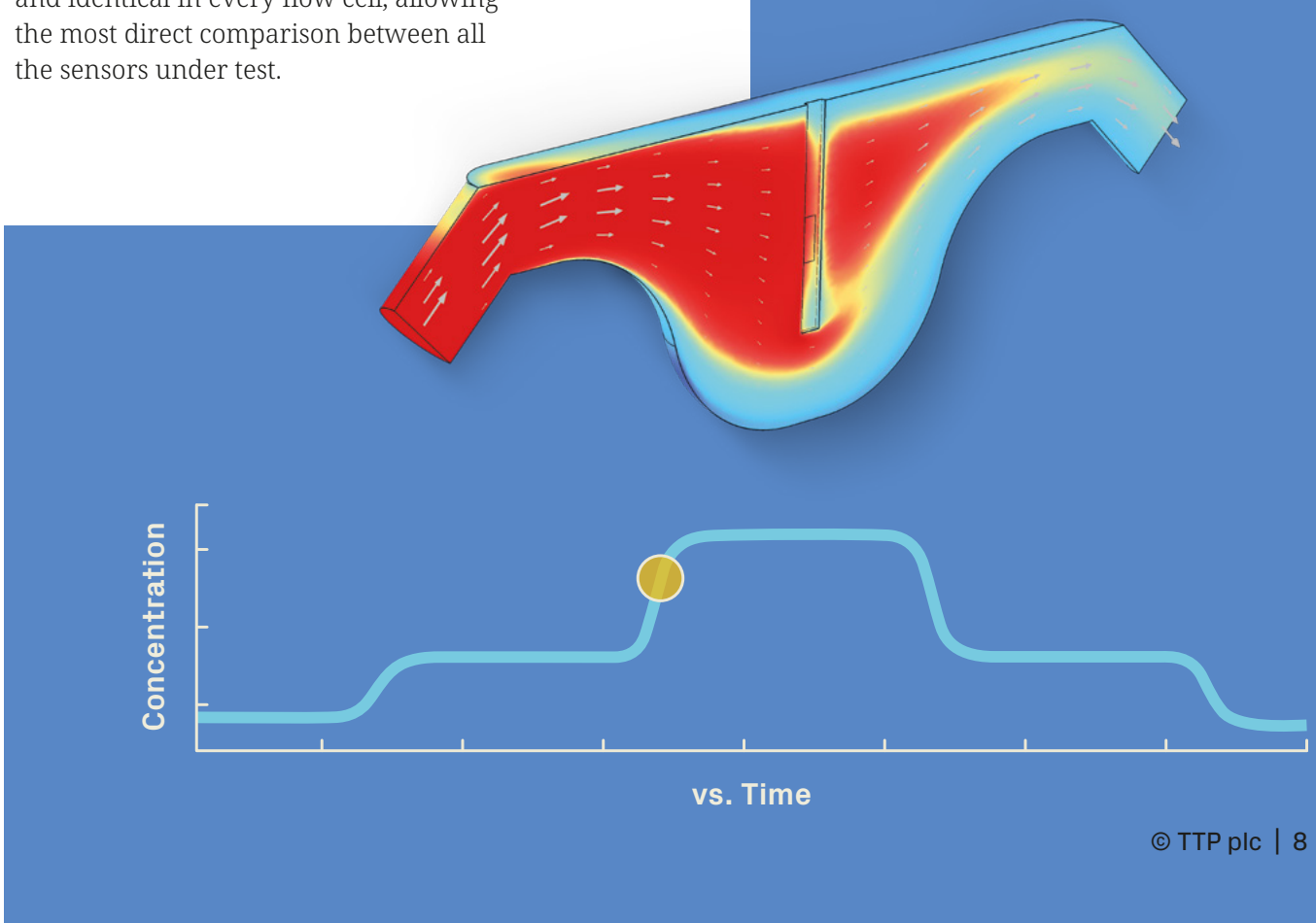


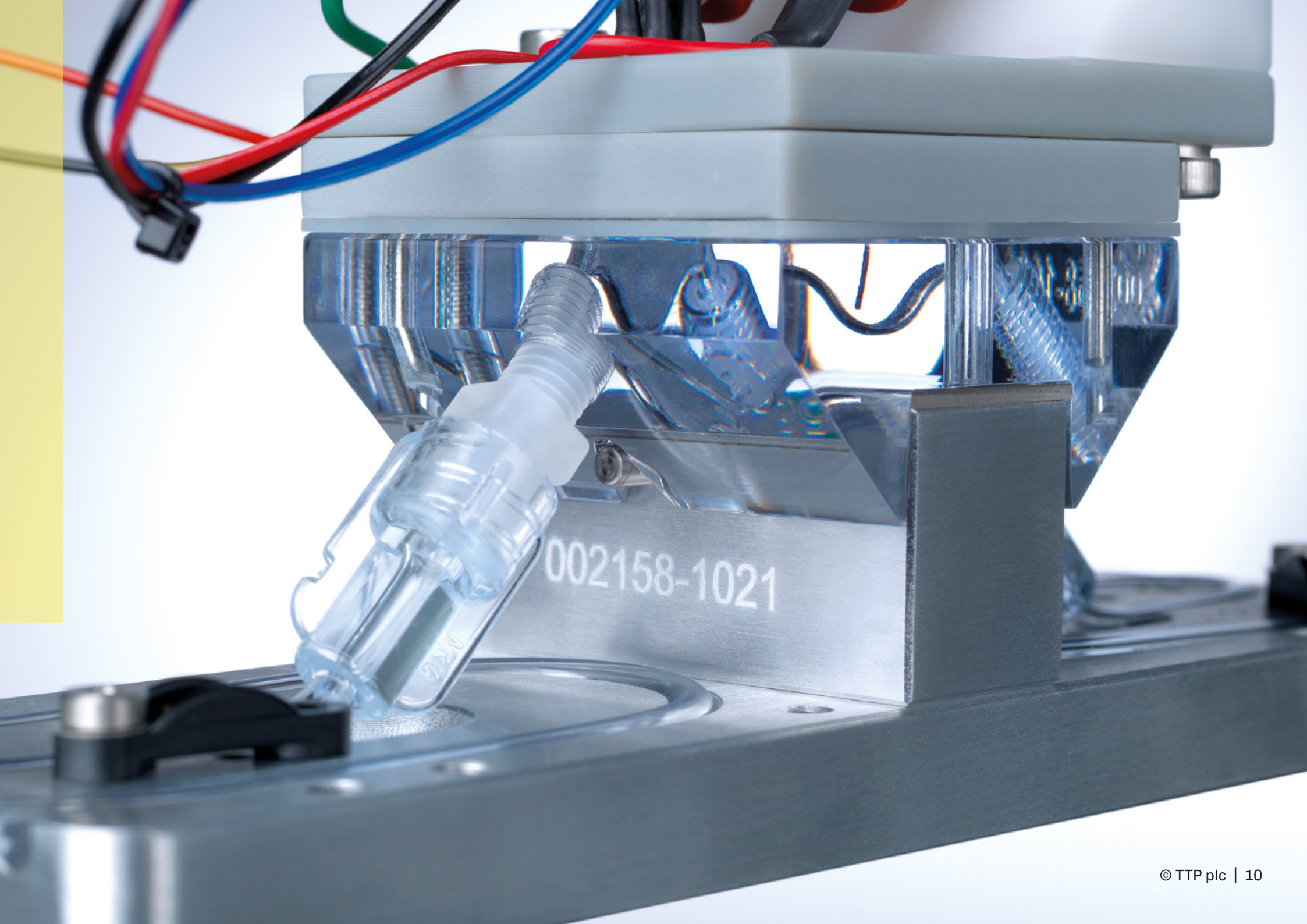
Figure 2:
Simulations were used to optimise the flow cell design for rapid fluid changeover.

CGM sensor mounting to support product development

To accompany the flow cell, the sensor mount and particularly the electrical interface are critical to support product development. Custom fixtures provide mechanical positioning, fluidic sealing during testing as well as shielded electrical contacts to external instrumentation.

This is not without challenges (such as long cables and careful design to minimise electrical noise), but it does enable sensor development to progress before electronics hardware development. Lab grade development instrumentation provides high quality data, which can be used to determine the right level of performance for cost-constrained production electronics.

TTP's CGM flow cell enables automated fluidics and interfacing with laboratory grade instrumentation.

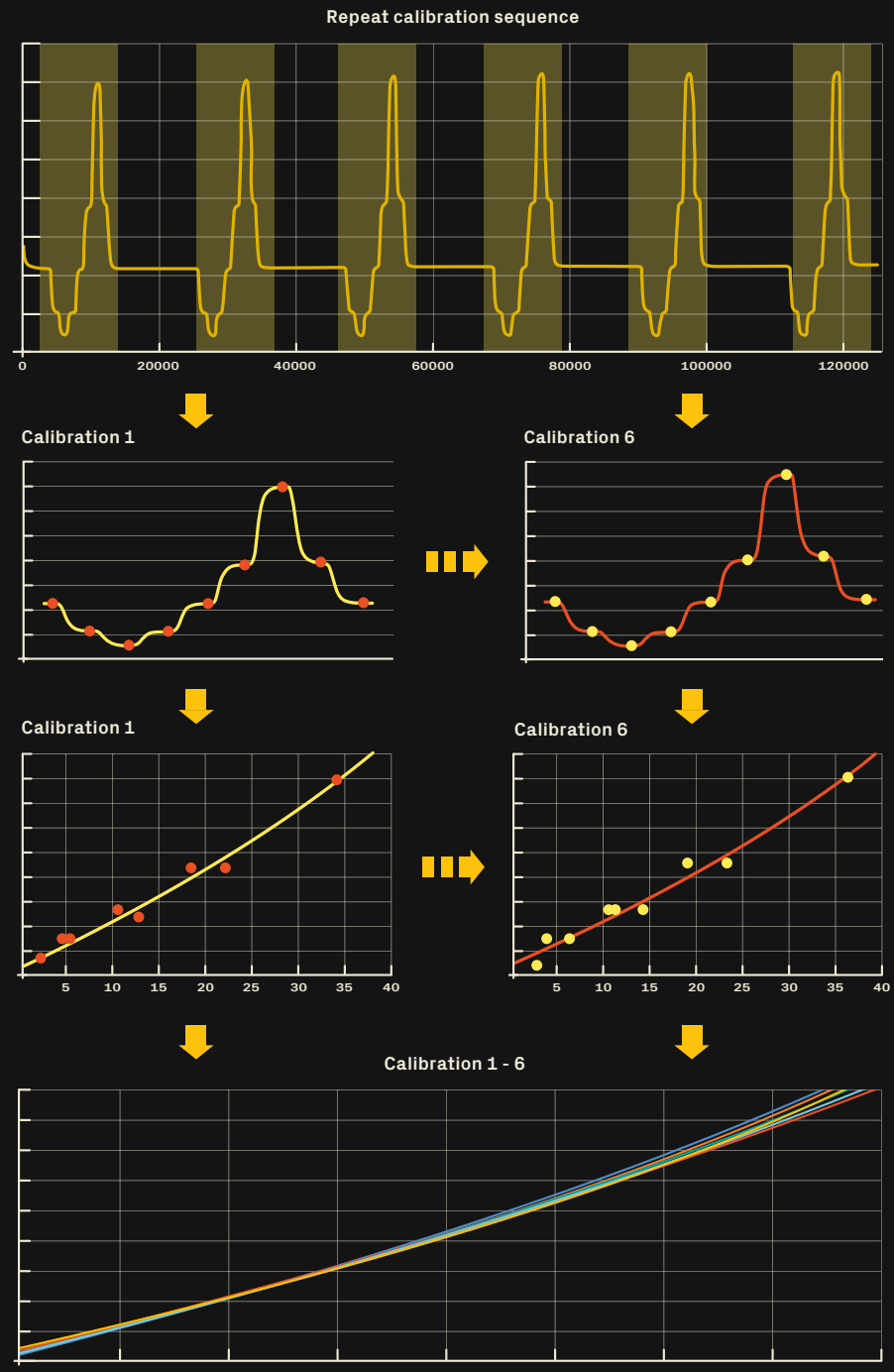

002158-1021

Demonstrating the performance of TTP's system fluids and measured sensor responses

Guided by reporting requirements for integrated continuous monitoring systems (FDA 21CFR862.1355), we chose 5 glucose concentration levels from 30 to 400mg/dL. We then used the measurement outputs to establish a calibration curve for the glucose sensor in question and to monitor small changes over repeated glucose step profiles. Here we show the results we obtained with premixed fluids, but dynamic mixing on-demand can also be used to generate concentration ramps to test the accuracy of rate of change measurements.

Using TTP's CGM sensor testing system can streamline the CGM development process.

Figure 3:
Automated calibration analysis can reveal subtle changes in sensor performance over time.



Analytics made simple

However meticulously recorded, sensor outputs are at risk of becoming useless without critical related data, such as sensor IDs (linked to design and build records), test fluids (with composition and batch traceability), test protocols, and test rig configuration.

We have developed a MongoDB database that links all this information to create secure, complete and accessible test records. Time-series sensor output data are automatically synchronised with fluidic and temperature logs and uploaded to the cloud-hosted database while the test is still running. This minimises the risk of data loss and allows real-time monitoring and analysis.

MongoDB's flexible NoSQL architecture can easily accommodate evolving requirements. It also enables standardised analysis procedures and cloud-based collaboration between sites and with external partners.

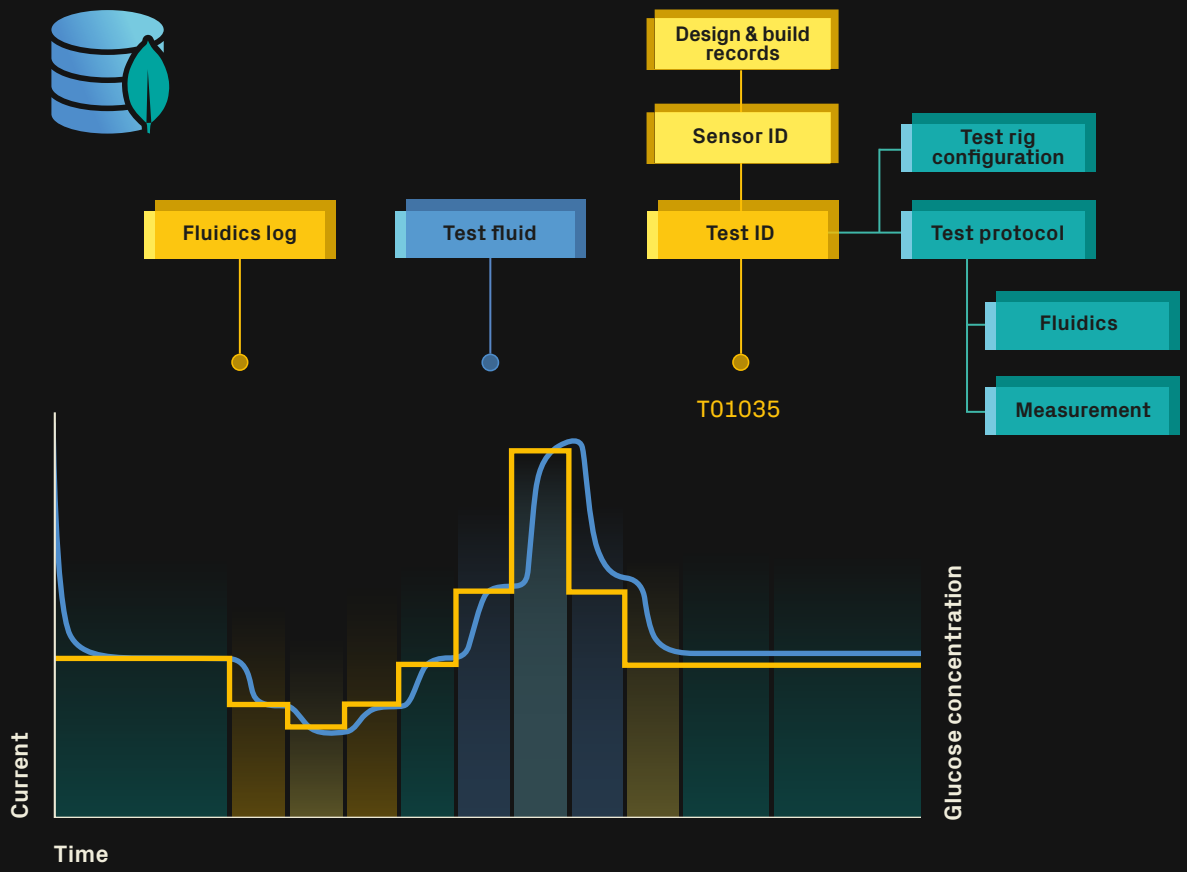
As the development of a CGM sensor progresses, the scalability of database storage becomes essential. The cloud-based architecture of our system allows expansion and a smooth transition from R&D to production.

One powerful feature of the database is the ease of carrying out virtual experiments: mining existing datasets to answer new questions that inevitably arise. For example, what was the impact of a change, whether deliberate or unintentional, in the manufacturing process? This system makes the data available to query and provide evidence, facilitating rapid and conclusive resolutions.

Using high throughput automated analysis, we can compare performance metrics across statistically significant numbers of sensors, revealing subtle features and allowing us to estimate the performance and yield expected from larger production batches.

Ultimately, the database provides a secure repository for the data that supports your regulatory approvals.

Figure 4:
Cloud database storage of sensor output data along with critical associated information enables traceable and automated analysis.



An adaptable platform that will meet your needs

Our platform meets all the needs of a typical sensor testing campaign, freeing up your time to optimise your core sensor technology.

TTP's CGM test system speeds up development by providing fluidic automation, sensor output measurement, and data management – all while maintaining flexibility and allowing rapid customisation where needed.

Please reach out if you want to learn more about the capability of our platform, or how it could be adapted to the needs of your CGM sensor.

About TTP's biosensing team

The automated CGM testing platform was developed by TTP's biosensing team. Specialising in the development of wearable and implantable biosensors, we deploy multidisciplinary project-specific teams combining capabilities from electrochemistry and optics to human factors, mechanical design, electronics, wireless power and communications, and software.

TTP – Expediting your journey from concept to clinical readiness.

References

1. [Online] https://diabetesatlas.org/#:~:text=Diabetes%20around%20the%20world%20in%202021:,risk%20of%20type%202%20diabetes..

2. [Online] https://diabetesjournals.org/diabetes/article/73/Supplement_1/1927-LB/154703/1927-LB-Impact-of-Continuous-Glucose-Monitoring

Let's talk.

Reach out to TTP's Biosensors team to learn more about how we can help you with your CGM development needs.

Get in touch

ttp.com

TTP plc
TTP Campus, Cambridge Road,
SG8 6HQ
+44 1763 262626

ttp.com