WHITE PAPER

Connectivity in the R&D Lab: Internet of Lab Things (IoLT)

Impact on Research Results, Instrument Performance and Productivity

Introduction

Connectivity is happening now, touching many essential parts of our lives—from the "smart" mobile phones we use to the servers where our data is stored. Additionally, routine signals are part of our daily interactions—everything from the traffic light, digital alarm clock, Doppler radar and household carbon monoxide detector. Imagine the possibilities if we open the aperture and now also collect all of the signals from connected devices. Enter the world of the Internet of Things (IoT), defined by devices intersecting with and exchanging data through the internet. The number of connected "things" is predicted to reach $30 billion by 2020[1, 2], with the potential of driving $3.9 to $11.1 trillion in economic impact by 2025.[3]

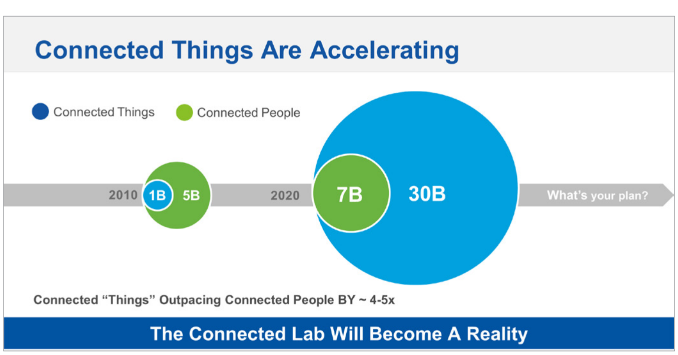

Figure 1. Connected "Things" Outpace Connected People by ~4-5x.

Changes driven by and derived from IoT are also occurring in the R&D lab. At its simplest, IoT applied to the Lab, or Internet of Lab Things (IoLT), refers to lab devices that communicate virtually and without constant human intervention. By enabling connectivity, IoLT captures lab-wide contextual data to reduce human error by way of autonomous monitoring and scheduling, and even protocol or instrument intervention for many remote tasks. For the R&D lab, IoLT value also encompasses the integration and sharing of device data such as operational and scientific analysis data.

While labs do not have to convert to the IoLT overnight, conversion is ultimately mandatory to remain relevant, improve time to market and increase efficiency. It is our premise that IoLT will continue to be an integral part of lab DNA and everyday researcher workflow. This paper will examine several of the opportunities that connected labs present.

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Background

IoLT-Influenced Error Reduction, Reproducibility Impact and Productivity.

Fundamental to lab workflows is the ability to impact research reproducibility. Irreproducibility indicates that research results could not be reliably replicated due to errors and omissions, as well as general lack of integrated and continuous data. Estimates are that the rate of irreproducibility in pre-clinical research exceeds 50% and that this phenomenon translates to direct costs of approximately $28 billion each year in the U.S. alone (Figure 2). The researchers who chronicled this problem found that of the total sum, 36% was attributable to mishaps with biological reagents and materials, 28% was linked to study design, 25% to data analysis and reporting, and 11% to lab protocols.

Researchers have found that irreproducibility is partly due to a lack of standard reporting methods. The National Institutes of Health (NIH) attempted to address this issue through the release of its "Principles and Guidelines for Reporting Preclinical Research."[5] Other groups setting standards are the Allotrope Foundation and the Pistoia Alliance, both of which are made up of many life science companies.

Still, irreproducibility is a challenge that one NIH action is insufficient to address. Overcoming the obstacle requires visibility to and capture of holistic lab data to help identify variables, isolate root cause, and document the paths toward effective discovery and downstream preclinical reuse.

Additionally, a trend noticed in the 1980s, dubbed Eroom's Law, indicated scientific discoveries becoming more expensive over time even as advanced methods and instrument technology improves (Figure 3).

IoLT-enabled and connected labs have the potential to address some of this root cause by capturing additive contextual data

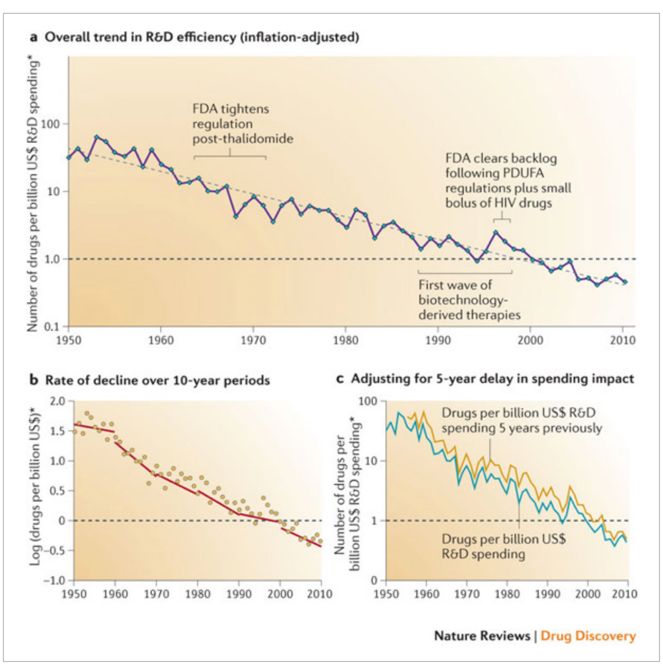

Figure 3. Eroom's Law.[6]

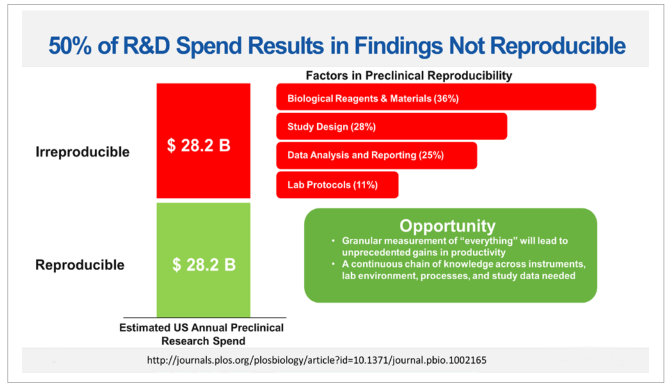

Figure 2. The toll of research reproducibility and main causes.[4]

that is often missing, thereby enabling automation, insights, and effective trouble-shooting. More precisely, IoLT impacts the following three value streams:

1. **Research reproducibility**
2. **Instrument performance**
3. **Asset and researcher productivity**

Figure 4 illustrates a variety of customer use cases enabled by IoLT Monitoring and Analytics. In this paper, we will examine several of these examples and how they relate to the three noted value streams.

Research Reproducibility

Given the cost productivity challenge from the lack of pharma reproducibility, there is an opportunity to realize high returns from improved collection of data. The opportunities to introduce errors and critical data inconsistencies are endless in the research and discovery process. With multiple therapies and experiments being run in the lab, on a variety of instruments by a variety of manufacturers, all with different service histories, the room for error is large. Lab staff may inadvertently mis document a result, or it may not be properly recorded in an electronic lab notebook (ELN) or LIM system. Added to this, lab micro-climate (in proximity to the instrument being used) environments are far from steady state, affecting results.

Environmental measurements that can be subject to cyclical changes from daily or seasonal effects include: temperature, humidity, light levels, air pressure. For example, geographic disparity for humidity was captured by Elemental Machines[7], who conducted a study where 219 sensors measuring temperature and humidity sensors were installed in labs throughout 37 different customer locations within the US. Locations were separated in 4 regions: North Central, Northeast, South, and West. Summary results are shown in Table 1.

Table 1. In many regions, humidity levels were outside of guidance for a portion of the year. Average Days per Year Laboratory Environment reaches <20% Relative Humidity.

Region	Avg Days <20% per Year
Northeast	80
North Central	36
West	12
South	8

Monitoring and Analytics Customer examples

	Monitoring			Analytics	
	1 Internal Asset Temperature / Humidity	2 Lab Environment	3 Instrument Performance and Location	4 Utilization	5 Maintenance Optimization
Customer Examples	**Monitoring freezer temperature** • Alert on weekend for high temperature • Repair completed before issue with samples **Monitoring incubator temperature** • Instrument showed incorrect temperature • Determined fan in incubator was faulty **Monitoring incubator humidity** • Alerted to humidity drop below 90% • Determined water pan was empty • Saved cell line **Monitoring ovens for temperature ramp** • Validate temperature ramp and cooling **Monitoring water bath for temperature** • Validate temperature stability	**Monitoring lab environment for humidity** • Low humidity drying out gel in assays causing repeat assays • Low humidity (< 10%RH) causing uncomfortable conditions for researchers **Monitoring lab environment for temperature** • Temperature at lab benches at windows 10 C higher than center of lab **Monitoring lab environment for pressure** • Monitoring pressure differential for positive pressure animal lab **Monitoring lab environment for light levels** • Monitoring light cycles • Workers turning on lights disrupting animals sleep **Validate new lab instrument installation** • New instrument not working as specified • Lab environmental conditions outside of specification	**Monitoring lab instrument repeatability** • HPLC erratic readout on peaks caused by HVAC blowing directly on instrument **Monitoring lab instrument for service issues** • Low humidity caused pipette tips sticking with liquid handling • High humidity caused corrosion related service issues • HCS autofocus complaints due to rapid temperature rise in room temperature **Monitoring Instrument location** • Instrument and component move to a new location • Before location services enabled Service engineer could not find location for PM **Monitor environmental conditions during instrument shipment** • Did not work on installation • Instrument stored on runway in high heat and humidity caused instrument failure	**Utilization for Lab Freezers** • Infer utilization of door openings via temperature profile analytics • Identified a freezer that was not opened and a candidate for relocation to high demand cold storage lab **Utilization for Lab Freezers** • High utilization provides justification for new CAPEX **Utilization for Incubators** • Infer utilization of door openings via temperature profile analytics • Identified an incubator not being used and candidate for relocation or decommissioning **Utilization for Centrifuge** • Infer utilization based on magnetic field monitoring • Low utilization candidate for relocation or decommissioning **Utilization for Ovens** • Infer utilization of door open event with analytics • Low utilization candidate for relocation or decommissioning	**Utilization for service optimization** • Low utilization provides justification to move off annual contract to time and material **Utilization for PM Schedule** • Use utilization to determine the number of PMs based on actual usage • Moved from time based to utilization based PMs **Monitoring freezer temperatures** • Average freezer temperature increase over a period of time • Determined defrost needed and validated average returned to normal **Monitor compressor cycles for refrigerator or freezer** • Alert to anomalies with compressor cycles using analytics **Utilization for Centrifuge** • Change service schedule from time based to utilization based for rotor replacement

Figure 4. Example use cases for Monitoring and Analytics in the IoLT.

Scientific equipment and, more importantly lab results, are very sensitive to these conditions. To address these concerns, manufacturers provide guidelines on the operating conditions. For example, a recommended range of 20-80% relative humidity is common. For most laboratories, temperature and humidity is measured and controlled to some degree. However, it is often the case that this control and measurement are not granular enough to identify microclimates within the labs. As illustrated by the Elemental Machines collected data, many labs have limited ability to modulate and control the variable humidity conditions.
As a result, laboratory humidity is significantly influenced by the local climate.

Use Case Hot and Dry Environments Impact on Liquid Handling Dispensing

We know that temperature and humidity can impact liquid handling quality.[8] This is especially pertinent to robotic liquid handlers for pipetting when operating in hot and dry environments. Figure 5 shows an example client operating a liquid handler in a lab that was well below specified operating conditions during the winter. This type of operating condition can cause under delivery by up to 35%.[9]

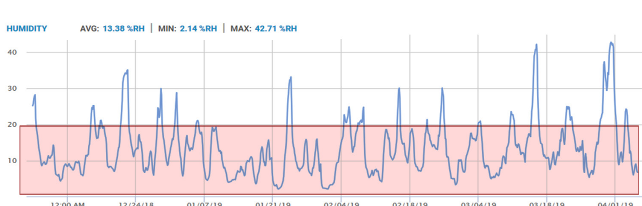

Figure 5. Example of Lab Humidity Values and Range.

Use Case Vivarium Mice Breeding

Staff in a lab responsible for breeding mice reported that births were not happening as planned. Unsure of the cause, the team implemented a wireless connected lab sensor to help determine the root cause. By examining the collected data and comparing it to a similar situation at another institution, the researchers concluded that the erratic reproduction was associated with the light and noise from nightly construction which was disrupting the sleep patterns.

Use Case Cell Line Growth and Incubator Monitoring

The advancement of cell biology and in-vitro research has been dramatic. With many drug discovery programs relying on cell-based assays, the need for properly functioning incubators has increased. This process starts with cell line growth and cultivation, which is carefully nurtured in a controlled incubator environment. Any significant changes to temperature and humidity can impact cell growth and respective phenotype, kinetics and assay performance. Cells can be in incubators for weeks to several months with values ranging from hundreds of dollars to priceless for donor dependent samples.

The assumption can be made that most incubators are qualified periodically (quarterly for temp and humidity and bi-annual for CO_2) to avoid erroneous Out of Spec (OOS) situations. But how confident are you that the calibration has not changed since the last event. In fact, a recent large Pharma client we are working with experienced incubator temperature drift as large as 4 °C from actual to panel displayed reading. This was observed, and action taken (samples moved and salvaged), from the installation of a continuous monitoring solution that caught and alerted on the discrepancy. In this case damage was alleviated with significant savings from "work-in-process" high value salvage of the cell. But what if the cell was grown to "maturity" without knowledge of the OOS condition with downstream use of "suspect" cells in a variety of related research?

Enhanced Benefits of Automate, Continuous Incubator Monitoring

- Maintain control and risk management of mycoplasma outbreak
- Continued calibration compliance
- Lab resource time savings from redeployment to other support activities
- Immediate and actionable response
- Monthly temperature and humidity stability reports
- Utilization metrics
- Automated reporting
- Dynamic, efficient and proactive programming

Instrument Performance

Instrument capital expense and ongoing operating maintenance expense are two of the high expense categories in the lab. Given the complexity and expense, most instrument manufacturers have detailed instructions for shipment, storage, installation, use and maintenance. These instructions will often include recommended environmental conditions such as optimal temperature and relative humidity for storage and use. These recommendations ensure consistent results as well as reduce service issues. Ensuring instrument uptime and optimal operation is a key driver for lab productivity. Monitoring instrument performance also eliminates a potential contributing factor to the research reproducibility challenge.

Example use cases for monitoring instrument performance in an R&D lab include:

- Monitoring and auditing relative humidity above 80%, which can cause corrosion on or within an instrument
- Monitoring and auditing relative humidity below 20%, which can introduce static electricity and impact liquid handling and balance/scale measurement
- Monitoring microclimates at instruments to help ensure consistent asset performance repeatability
- Monitor temperature in the lab for potential service issues with instruments
- Validating environmental conditions for new instrument installation
- Monitoring environmental conditions during shipment to ensure the instruments are ready for installation and validation when they arrive

Use Case **Mass Spectrometer**

A testing lab in a remote location was experiencing performance issues and repeated downtime with a mass spectrometer. After repeated service visits, it was decided to closely monitor the lab temperature with sensors that could be monitored remotely and seamlessly without manual inspection. The data showed intra-day temperature variability from 22 °C in the morning to 35 °C by the end of the working day. The high temperatures were contributing to the issues as the recommended temperature for operation was between 20-25 °C. Additional cooling was added to the lab to correct the temperature.

Use Case **Automated Liquid Handling**

A large pharmaceutical company experienced an unusual amount of downtime due to service issues for several liquid handlers in one room within a large lab. Service issues did not consistently occur, but rather, were more pronounced just during some days in the winter months. One of the common issues was tips sticking. One extreme issue resulted in one of the pipetting heads breaking. Several environmental sensors were placed in the room in close proximity to the liquid handlers. After a week of data collection, it was observed that humidity was consistently below 15% RH with lows of 5% RH. The recommended humidity for the liquid handlers was above 20% RH on the low end.

Use Case **HPLC Variability**

Sunovion Pharmaceuticals[10] was experiencing erratic output results from one of their HPLC instruments. The series of peaks was jumping around on the instrument's readout. After weeks of troubleshooting and researcher engagement, they deployed wireless, connected temperature sensors near the unit to measure the microclimate. They quickly realized that the cause of the instability was due to a HVAC system that was intermittently blowing hot air on the system and causing out-of-spec operating conditions. Once they took into consideration the temperature fluctuations, modifications to their workflow resolved the issue with the HPLC.

Asset and Researcher Productivity

An important lab operations and researcher question is, "how can I better leverage scientist time?" With IoLT sensors, menial and repetitive tasks such as documenting environmental or specific asset conditions can be automated. By automating these tasks, researcher can focus on higher value work. Asset productivity is also improved by capturing, aggregating, and analyzing connected data related to how used, when used, where used, how often used, and under what environmental conditions. Poorly operating assets can be decommissioned, saving maintenance and operating costs. Underutilized assets can also be repositioned to other high throughput labs perhaps saving the capital expense of a new system. Additionally, instruments can be scheduled and optimized to operate during certain times to maximize productivity.

Example use cases for improving asset, supply chain and researcher productivity in an R&D lab environment include:

- Monitoring cold storage equipment
- Monitoring incubator environmental conditions
- Using asset utilization to optimize preventative maintenance schedules and frequency
- Using asset utilization to relocate or decommission assets
- Traceability of reagents from origin to customer
- Tracking temperature, humidity, and exposure to light for reagents

Use Case **Freezer Monitoring**

A research lab was monitoring temperatures of their 40 refrigerators and freezers using data loggers. Twice a day, including weekends and holidays, researchers were required to walk over to the freezers, read the temperature off the data loggers, and then record the value, time, date, and their initials in a logbook. If a freezers temperature is outside predefined parameters, an alarm would sound (of course this required someone to be in the lab to respond).

A new approach was deployed with sensors for refrigerator and freezer monitoring, with data recorded automatically every 15 seconds, 24 hours a day, 7 days a week. Notifications of potential issues were automatically sent via email and text to the refrigerator/freezer owners.

ROI - This resulted in returning over 450 annual hours back to the research team. Automatic data collection notification also saved researchers from having to be in the lab during weekends and holidays.

Use Case **Freezer Utilization**

A testing lab had 75 refrigerators and freezers for sample storage. The lab manager theorized the configuration and location of the freezers was the root cause for some being underutilized while others were experiencing enormous usage. The current system only monitored temperature and had no utilization related information on how often the freezers were being opened. New wireless IoT temperature sensors were installed on several of the units. Leveraging temperature profile analytics, door opening events were inferred. The results showed one freezer was opened 185 time in one month, with an average temperature of -67 °C. Another freezer of the same type was opened seven times in one month and had an average temperature of -78 °C. Additionally, one freezer had not been opened during the past month.

ROI - Freezer not opened can be decommissioned
$ 2,000 annual maintenance contract
$1,000 annual energy cost
5 SQFT returned to Lab

ROI - Relocate freezer saving capital expense for new freezer
$15,000 new freezer cost.

Figure 6. Example of an IoLT enabled lab.

Use Case **Incubator Monitoring**

A research lab had several incubators that were checked daily for temperature and humidity. The check for the humidity required the incubator to be opened and a visual water level inspection of the water pan to maintain the required 95% humidity. Unfortunately, the responsible inspection person got ill, was out for a time, with no identified replacement. This resulted in several incubators running out of water resulting in humidity well below 95%. Temperature and humidity sensors were installed in the incubators allowing alerts and notifications to be sent to multiple people when any temperature or humidity thresholds were exceeded.

ROI - This resulted in returning over 250 annual hours back to the researchers.

Use Case **Centrifuge monitoring**

A research lab had hundreds of centrifuges scattered throughout one lab campus. The annual maintenance spend on these centrifuges was greater than $100,000. A significant part of the spend was on preventative maintenance (including periodic rotor replacement) that was done on a calendar basis regardless of centrifuge usage. By monitoring centrifuge utilization, maintenance was moved to "on-condition" with results indicating 15% of the centrifuge fleet having very limited usage.

ROI - 15% reduction in maintenance spend for centrifuges Return a percentage of bench space back to the lab for other use.

Use Case **PC Controlled Assets Compels System Utilization Capture**

A large Pharmaceutical company as part of a system replacement and upgrade campaign decided to monitor and analyze utilization across several of their high end systems, mostly liquid chromatography/mass spectrometry (LC/MS), at a site. It quickly surfaced that several systems were not highly used and an opportunity to reposition these assets as opposed to purchasing new was realized.

ROI - In some cases they were able to show that a 1 for 1 replacement strategy was not prudent. Because utilization data was available, a 1 for 2 or 2 for 3 retirement/replacement strategy was used, with enough capacity to meet the analysis throughput demands of the lab.

Use Case **Traceability of Reagents**

Manufacturers of reagents guarantee the reagents only if they have been shipped, stored and handled according to their requirements. When reagents are in transit from the manufacturing site to the customer, there can be gaps in the environmental conditions. Once at a customer site, they may be left on a loading dock or other location without the proper storage. Without environmental-condition visibility throughout this process, reagents may be compromised, requiring the entire experiment to be repeated. With sensors that measure environmental conditions these gaps be closed, providing a complete view of conditions from the point of origin to their use.

ROI - Cost of replacing reagents Eliminate repeating experiments due to compromised reagents.

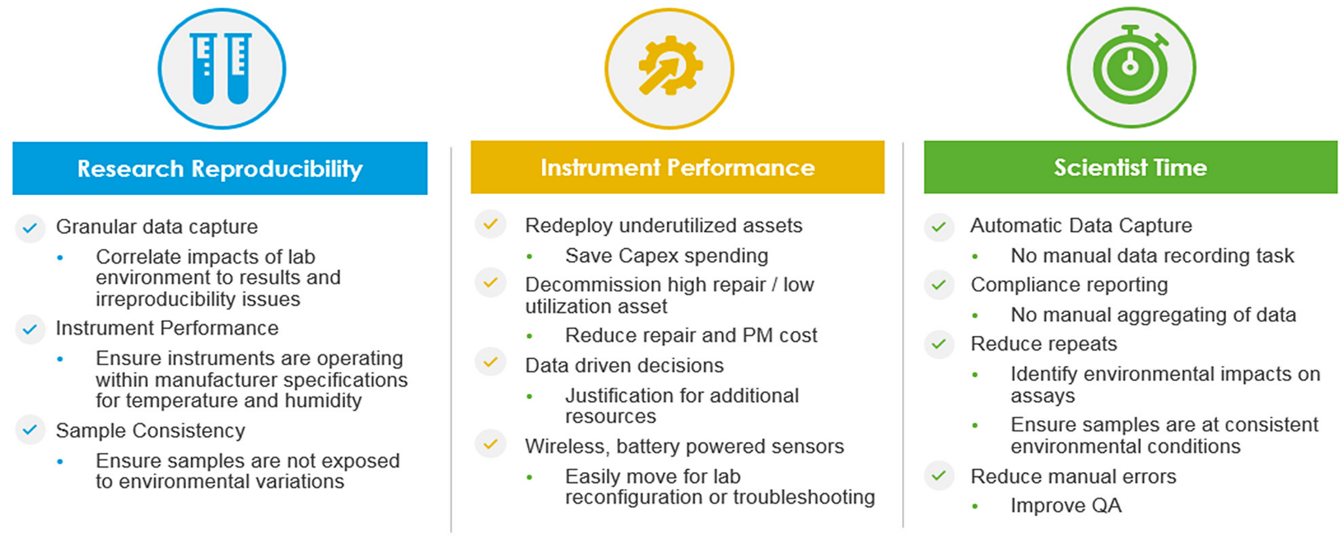

Figure 7. Summary of discussed benefit areas.

Conclusion

The time for IoLT is now. By taking advantage of new connected technologies available for the lab, organizations will see increases in research reproducibility, instrument performance and researcher productivity. Combined, these will result in a decrease in costs and an increase in ROI. Automated and continuous monitoring controls and reduces risk, and provides the basis for dynamic, efficient, and proactive programs. IoLT enables the situational awareness, true consistency, and adaptability needed in today's R&D lab to support reproducibility and productivity to facilitate breakthrough science faster.

PerkinElmer is helping facilitate this journey to a new normal, helping labs drive efficiency in operations using productive innovations that lead to consistent productivity across the board.

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