Storing Corneas — Innovations in Environmental Monitoring Solutions

Michael Rusnack,[1] Thomas D. Miller, CEBT,[2]

ABSTRACT

The evolution of sensing technology has experienced significant change with the advent of low-cost, integrated electronics. Inexpensive microcontrollers with integrated data conversion technology have resulted in the smart sensor becoming increasingly more affordable. With this technology, coupled with the internet's pervasiveness, a new era of sensing technology is ushered into use. It is referred to as IoT (Internet of Things). These devices are now being configured to communicate to cloud-based servers, eliminating the need for hardware to be installed locally. With cloud storage and the available computing power in the cloud servers, both artificial and business analytics may be applied to the collected data.

The objective of the monitoring solution is the first and foremost accurate representation of the cornea temperature. The monitoring process, recordation, and display of the collected data trending and alert notification based on the trending are necessary. Equally as important as the accurate representation of the cornea tissue temperature is reliable alerting. False-positive alerts cause alert fatigue; missed alert conditions can result in cornea tissue being compromised.

Key Words: Temperature Buffer, Virtual Temperature Buffering, Cornea Chamber, Temperature Monitoring

This paper explores the tools available for data collection, the methods for accurate representations of the collected data, and an introduction into the analytics that can be derived from the data stream.

PURPOSE

The environmental monitoring system currently in use by eye banks for controlled storage of corneas includes a NIST traceable, calibrated thermometer in the storage unit. A more sophisticated solution may consist of a recording device. One is a disk wheel, an advanced solution that consists of an electronic device connected (directly or indirectly) to a server where the data is stored and managed.

With the introduction of the Internet of Things (IoT) devices, the opportunity for continuous monitoring becomes more cost-effective. These devices are typically small, self-contained, and cost-effective methods that often will utilize wireless communication technology. Wireless communication will, in most cases, employ industry-standard technology such as WiFi or cellular communication protocol.

The consequence of improper storage and the effects observed on the human cornea is well understood.[1] The best assurance of the cornea viability is to understand the storage conditions that the tissue had experienced. Manual recordation is only a spot check, whereas continuous monitoring summarizes the entire storage period.

Continuous, real-time monitoring provides the end-user with an accurate representation of the storage conditions. It is quite common from that data stream to set control limits for the temperature; for example, when exceeded, the user is alerted. The alert notifications are carefully established to protect the corneas from damage while not overtaxing the end-user with excessive alerts.

With the availability of real-time temperature monitoring and cloud computing applications, cornea tissue storage management can be improved. These solutions result in greater efficacy of the stored materials while preventing loss of this precious material.

METHOD

Current storage environment monitoring at eye banks differs slightly depending on the facility, while most adhere to the Eye Bank Association of America Medical Standards on tissue storage.[2] These standards include having a NIST

Author Affiliations: [1]Vice President, Science & Engineering, American Pharma, Boise ID [2]Vice President of Quality Assurance and Regulatory Affairs, CorneaGen, Seattle WA

  ISSN 2161-5546

traceable certified temperature monitoring device visible from outside the refrigerator, a temperature buffering capacity that accurately reflects the temperature of stored tissue, and a daily record of all temperature excursions.[3] Logs are maintained of recorded temperature for reporting and analysis. With the power of cloud computing (remote servers), data and business analytics may be applied to the recorded data.

The most significant advantage of these systems is their ability to continuously monitor conditions with intelligent software on a remote server and alert responsible personnel over the Internet with SMS, text, email, or voice call. The alerting can be tuned to respond instantly upon a temperature excursion or delay a fixed duration, ensuring a false alert is prevented. This ensures that no temperature excursions are missed and all such events are handled promptly. When adequately programmed and validated, the software can differentiate between temporary "normal" events due to compressor cycles and actionable events due to equipment malfunction or mishandling.

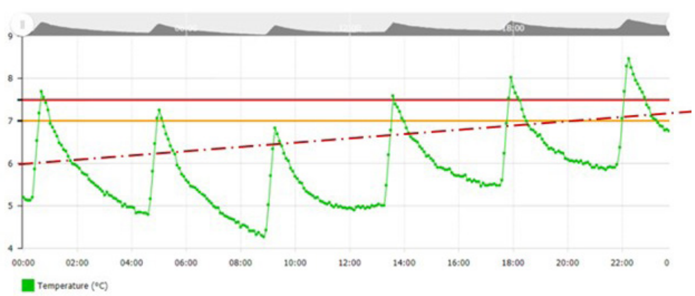

***Figure 1:** Temperature Excursion Due to Storage Unit Malfunction*

The figure above is the display trace of a continuously monitored storage unit. The centerline trend is an indication that this unit requires maintenance. Without continuous monitoring and the representation above, the awareness of an issue may not be apparent. Furthermore, the ability to diagnose the problem is very much simplified through the graphic display above.

Sensor Deployment

It is a common practice to place the measurement sensor into a buffering medium. This practice aims to "slow" the rate of change of the storage unit temperature environment. A typical use of a temperature buffer is to prevent the inrush of warm air when accessing the storage unit from triggering a false alert.

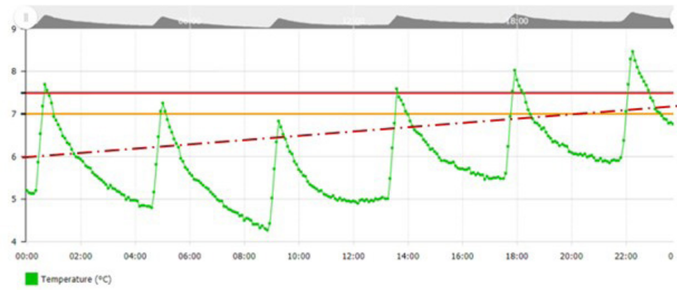

***Figure 2:** Temperature Excursion Due to Storage Unit Access*

Figure 2 above captures an excursion event due to the inrush of warm air when the storage unit door is opened. The green trace (measured temperature) is observed exceeding the upper control limit (red control line). The purple trace is the air temperature being "slowed" by a 20ml buffer. The system eventually alerted after a long duration after the door was opened and maintained open.

At times, the use of a thermal buffer may conflict with its intended use. As noted above, the buffer's purpose is to "slow" the rate of change of the measured air temperature of the storage unit. The second and often conflicting use is the accurate representation of the cornea tissue.[5] The optimal solution is to accurately represent the cornea tissue in size, geometry, and content. This approach's result is the assurance that the reported temperature is correctly representative of the stored cornea.

RESULTS

The results from both of our small and large-scale studies provided the necessary validation needed to support the patented algorithmic replacement of a physical buffer. From the raw air temperature, the effect of the temperature can be modeled for not only the cornea chamber and vial but might also be used to model for any temperature-sensitive product. The use of expanded analytics and artificial intelligence goes well beyond simple temperature measurement and recordation.

Using a continuous monitoring system and algorithmic replacement of physical buffers is a best practice and would significantly improve US eye banks to improve current practices for environmental monitoring. These improvements may also more effectively satisfy the FDA, and EBAA recommended practices for tissue storage, reduce waste, and enhance corneal tissue safety and efficacy for transplant accordingly. The authors suggest that the EBAA

Medical Advisory Board consider this option one best practice for storing and monitoring corneal tissue.

DISCUSSION

The EBAA Medical Standards guide the proper storage and maintenance of corneal tissue. This document provides a direction; however, that is lacking in the specifics of the implementation, which can create confusion. The purpose of this paper is to help clarify and provide recommendations to meet the guidance described in this document concerning the application of virtual temperature buffering (algorithmic buffering) as a valid option.

A fixed buffer assumes that the entire content is a single volume and geometry, which is rarely accurate. With the application of a virtual temperature buffer, one can accurately simulate any volume and shape that is maintained in the storage unit. With virtual buffering, the effect of an excursion can be correctly applied independently to each volume rather than a blanket assumption that all volumes are affected the same.

EBAA Medical Standard C3.200 Equipment Maintenance and Cleaning describes the standards for the monitoring of the refrigeration unit. A key provision of this section is the following statement:

> "The temperature recording device should reflect the temperature of the stored tissue under normal storage conditions."

The need serves two purposes:

To best represent the stored tissue, a thermal buffer is necessary. The buffer dampens any air temperature changes when the storage cabinet is accessed, and as stated, it reflects the actual temperature of the stored tissue.

The EBAA approach to tissue storage is a conventional practice with similarities as in vaccine storage, which is to insert a temperature probe into a bottle of glycol or equivalent thermal buffer medium. The Glycol bottle's purpose is to stimulate the stored material's temperature experience rather than just the air temperature. Such a thermal buffer is intended to reduce false alarms so that the manager will know with higher confidence that a temperature alert is an event requiring action.

The conventional method for buffering the temperature in a cornea viewing chamber or glass vial is to place a temperature probe is inserted into a like container and have the entire contents placed into the storage unit. The storage chamber or vial is often subject to spillage, damage and, at times, can be cumbersome to set. Glass beads, nylon, and metal blocks are also alternatives to the liquid buffer that decreases spillage issues. These methods have a similar problem: they are cumbersome compared to the temperature probe. When placing a physical buffer, the size results in the buffer often being placed on the bottom of the storage unit. This action can and will result in more significant buffering than intended.[6]

Therefore, the aim would be to have processes and units available inside a refrigerator allowing local assessment of temperatures, which are adjusted long-term inside stored tissue. It is the objective to represent the tissue's temperature being held, not just the tissue's environment. Two temperature probes were placed to record the air's temperatures and that inside of a 20-ml cornea chamber to demonstrate the efficacy of the technology. The air temperature data is utilized to compute the equivalent algorithmic buffer values. The actual and comparable corneal chamber measurements can then be compared.

The intent was to model the contents of the stored tissue closely. Mathematical modeling allows for approximating the impact of temperature on tissue inventory while providing the ability to model differing volumes and shapes of storage containers in the same storage unit. The mathematical model begins with the solution of the equation described below.

Virtual Temperature Buffering

One solution to the problems identified above is a concept called "virtual buffering." This method involves a mathematical calculation to compute the temperature inside a known material container based on the thermodynamic equations and the surrounding air temperature.

The calculations involved with this method are not complicated and are shown on the following page

$$\frac{dQ}{dt} = C_p A \frac{d}{dt}(\Delta T)$$

Cp = thermal conductivity constant

A = describes the stored container geometry

dΔT/dt = Temperature gradient

dQ/dt is proportional to T0 - $T_{ambient}$ and Cp A are constants

$y(t) = T(t) - T\infty$ Temperature difference between stored medium and air temperature

$y(0) = T(0) - T\infty = To - T\infty$ Initial temperature difference at t=0

$$\frac{dy}{dt} = \frac{d}{dt}(T(t) - T_\infty) = \frac{dT}{dt} - \frac{dT\infty}{dt} = \frac{dT}{dt} = -k(T_o - T_\infty) = -ky(t)$$

$$\frac{dy}{dt} = -ky(t)$$

$$\frac{\frac{dy(t)}{dt}}{y(t)} = -k$$

$$\int \frac{\frac{dy(t)}{dt}}{y(t)} dt = \int -k\, dt$$

$$\ln(y(t) = -kt + c = c - kt$$

$$y(t) = e^{C-kt}$$

$$y(t) = ce^{-kt}$$

$$c = (T_o - T_\infty)$$

$$T(t) - T_\infty = (T_o - T_\infty)e^{-kt}$$

$$T(t) = T_\infty + (T_o - T_\infty)e^{-kt}$$

Equation 1 Algorithmic Buffer Equation

From Equation 1 above, an algorithmic model can be used to predict the thermal response of any shape, volume, and material while using only air temperature. It should be noted, using the above method in bodies of simple geometry, e.g., cylinders, spheres, the error introduced by the assumption of uniform body temperature will be less than 5%. (Bergman, 2017) This formula was tested by comparing the theoretical data using Equation 1 and physical glycol buffering of the same size. The result was as the model predicted; the error was observed to be +5% / -3%. As demonstrated in an independent study, the accurate derivation of the constant k results in a much more accurate representation of the stored contents' temperature with an error of 0.5%. With the ability to represent the cornea tissues' temperature while providing an equivalency of buffering the air temperature, it is no longer necessary to utilize a physical buffer. The recorded raw air temperature can be acted upon, providing data that a buffered temperature would otherwise mask.

The constant k is a unique value, in this case, for the 20-ml corneal viewing chamber or glass vial that is typically used. Initial testing included a single cornea chamber and an air temperature probe. The subsequent analysis included the deployment of the same apparatus in multiple and different storage units. It was necessary to verify the operation is a laboratory environment and in storage units that are accessed as part of the typical day-to-day process. Extensive testing and analysis comparing the actual temperature of the cornea chamber to the computed value. The data sets were statistically compared; the correlation between the two data sets was found to have a Pearson correlation coefficient value of 0.99112, a strong indication of equivalence.

To demonstrate the efficacy of the technology, two temperature probes were placed to record the air's temperatures and that of a 20-ml cornea chamber. The air temperature data can be utilized to compute the equivalent algorithmic buffer values. The actual and comparable corneal chamber measurements can be compared on a single graph. In Figure 3, the air temperature is shown with the results of the algorithmic representation of the 20 ml cornea viewing chamber or 20 ml glass vial with storage media.

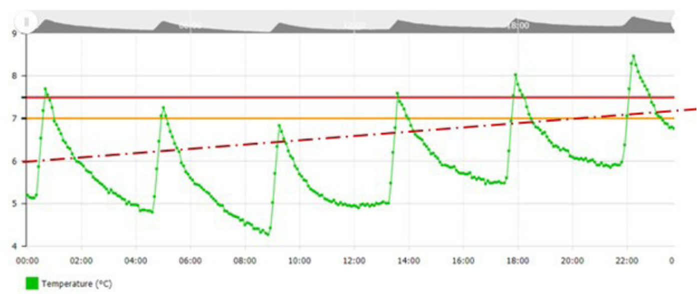

Figure 3: *Virtual 20ml Cornea Chamber*

Beyond Virtual Temperature Buffering

By retaining the raw air temperature data, further business and data analytics may be applied and evaluated. The raw air temperature can be acted upon by noting trends and deviations from those trends. This data can be used as a predictive model for pending failure or need for preventive maintenance.

There are three (3) factors that may be evaluated in the analytics. Each category can be broken into finer points. Each point can be given a performance score. These performance scores can then aid in the evaluation of overall system use and performance.

1. Human Factor – Describes the interaction of the uses with the system T*he individual and composite scores indicate how the system is being utilized on a prescribed basis, i.e., User Check-in completion, Alert acknowledgment, and resolution.*
2. Machine Contribution – Describes the performance of the storage unit. *The storage unit's operating performance is an indicator of the storage conditions the cornea tissues are being subjected to, i.e., temperature excursion range, time outside of the control limits, and alert frequency.*
3. Environmental Contribution – Describes the impact of the outside factors on the storage system. *The environmental conditions that influence the storage system are often overlooked, i.e., AC power reliability, communication quality, facility environment (temperature)*.

These examples are only a small handful of analytic tools that may be employed when acting on the raw air temperature. Once a buffer medium modifies the air temperature, valuable information is lost.

REFERENCES

1. Jun.Armitage WJ. Preservation of human cornea. *Transfus Med Hemother*. 2011;38(2):143–7.
2. American Academy of Ophthalmology. EBAA - Medical Standards. Washington DC; 2017
3. Eye Bank Association of America (EBAA). Medical Standards. Washington DC; 2013 Nov.
4. Incropera FP, DeWitt DP, Bergman TL, Lavine AS. *Fundamentals of heat and mass transfer.* 6th ed. Nashville, TN: John Wiley & Sons; 2006.
5. Rusnack MR. Accurate Temperature Representation of Cornea tissues Using an Algorithm as a Replacement for a Physical Buffer. In: NCSL International Workshop & Symposium | Measurements of Tomorrow Portland.
6. Rusnack MR. Misuse and Misconceptions of Physical Temperature Buffering. In: NCSL International Workshop & Symposium | Cleveland. 2019.