Improving Vaccine Safety by Using an Algorithmic Model as a Replacement for a Physical Thermal Buffer

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ABSTRACT

Conventional practice in vaccine storage is to insert a temperature probe into a bottle of glycol, or another equivalent thermal buffer medium, to simulate the temperature experience of the stored vaccine, rather than just the air temperature. Such a thermal buffer is intended to reduce false alarms so that the drug manager will know with higher confidence that a temperature alert is an event requiring action. While necessary and appropriate to correctly monitor the storage conditions, it is a practice that is messy, inconvenient, and costly, and can result in reports that diverge from the actual experience of the stored inventory. This paper explores the use of a mathematical algorithm to reproduce the behavior of a physical thermal buffer medium. The paper describes the algorithm and reports the degree to which it accurately simulates the experience of a 20-ml glycol container. The algorithm is shown to be highly predictive of the temperatures measured inside a container containing glycol.

Keywords: Algorithm Buffer, Glycol Monitor Storage Vaccine, Monitor, Buffer, Vaccine, Glycol, Algorithm, Storage

Introduction

Vaccines containing live viruses must be frozen until they are administered to maintain efficacy. Likewise, refrigerated vaccines must be maintained within the prescribed temperature limits. Improper transport and storage can cause vaccines to become inactive or contaminated, compromising their efficacy and possibly posing a threat to public safety.[1]

To ensure that vaccines are not damaged or compromised the Centers for Disease Control and Prevention (CDC) have issued protocols to ensure proper handling, which specifies that the temperature of stored inventories must be regularly and accurately monitored to ensure that the vaccine temperature remains within specified limits.[2,3]

Temperature monitoring is complicated by the fact that the raw data received by the thermistor in the refrigerator can be misleading. An unweighted temperature probe e.g. unbuffered) will react much more quickly to the effect of opening a refrigerator door than will the vaccines stored in the refrigerator. To correctly monitor inventory potency, it is essential to know, as closely as possible, the internal temperature of the stored inventory rather than simply measuring air temperature around them.

To address the problem, the CDC has recommended that the temperature data from the probe be weighted by immersion in a thermal buffer such as propylene glycol. This provides a somewhat more accurate understanding of how the inventory within the storage compartment is being affected by door openings, power loss, compressor on/off cycles, and other events that affect air temperature.[4]

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However, liquid glycol is not ideal for this purpose because it can be affected by several variables that are difficult to control and monitor. For example, glycol can dissipate or be accidentally spilled, changing the effective volume of the buffer over time and therefore its responsiveness to changes in air temperature. Glycol bottles can be improperly positioned or inadvertently moved to locations that impair their performance, such as when placed in physical contact with another container or a refrigerator wall. Given the size and shape of the glycol bottle, the likelihood of contact with the contents or structure of the storage unit is greater than an air probe. This contact alters the physical properties of the glycol bottle. Often a glycol bottle of one volume and shape is used when the vaccine is stored in a container of a completely different size and shape. Further, the thermal response of glycol is not identical to that of vaccine fluid. All these conditions can adversely affect the accuracy of the temperature measured by the probe, leading to inaccuracies that can result in undetected, undocumented, and unheeded temperature deviations.[5] For comparison purposes, other volumes such as syringes, cuvettes, and other vaccine containers were compared against the "standard" glycol container. Any modification to the buffering media through loss of volume, contact to the storage unit surfaces or contents will result in a change to the buffering capacity. Other buffering media, such as sand or glass beads, can be used instead of glycol, but their use mitigates only the first of the problems identified above (evaporation, spillage, etc.). Additionally, acquiring, installing, and maintaining the liquid glycol adds additional cost and can be inconvenient. These factors point to the need for a more convenient and reliable method.

The solution evaluated in this study is an innovative and novel approach to replicate the behavior of a physical thermal buffer with a mathematical algorithm. Using a single air temperature probe located in the center of the storage space and knowledge of the measured temperature response of the physical buffer to changes in the air temperature, mathematical analysis is applied

to the data to predict the response of the physical buffer to changes in the air temperature.

The purpose of the study was to determine whether such a mathematical algorithm could reliably and accurately predict the temperature in a physical buffer, including reactions to various types of changes in the air temperature, e.g. temperature cycling fast and slow and temperature excursion.[6]

Materials and Methods

The mathematically computed temperature was derived from the following algorithm, along with the appropriate constants:

$$PT(t) = Ta + (To - Ta)\, e^{-(A/k)M}$$

PT(t)	Predicted Glycol Temperature at time t
Ta	Air temperature at time t−1
To	Air temperature at time t
A/k	Cooling / Warming constant
M	Minutes between Ta and To the raw data received by the thermistor in the refrigerator

The performance of the algorithm was tested by taking temperature readings from two temperature probes every five minutes for a three-day evaluation period. Accurate representation of the temperature of a refrigeration unit requires proper sample rate. Using Fourier (FFT) and Nyquist-Shannon Analysis, it was determined the optimal sample rate of one sample per every 10.8 minutes was necessary to accurately capture the full data stream. To be conservative, a sampling rate of one sample per five (5) minutes is chosen as the best representation of the sample rate.[7]

The data collection system included a single Wi-Fi enabled radio monitor with a dual input. The probes were placed in a refrigerator in a functioning clinic where the storage unit was accessed regularly as part of the day-to-day operation. The unit was a large capacity two door refrigerator with an operating range of 2 to 8°C. One probe was in the center of the storage unit and measured air temperature; the other was immersed in a 20-ml bottle of glycol also located in the center of the storage unit. The air temperature data were subjected to the algorithm and recorded. The two data streams representing physical and algorithmic glycol were then compared for this study.

The refrigeration unit was fully stocked with vaccines and other pharmaceutical materials. During the entire period of the study, the refrigerator was accessed regularly as one would in normal use. Each thermistor was encapsulated in a 1" x 0.125" stainless steel extrusion. The thermistors were inserted into a 3-inch-long stainless-steel case and secured with epoxy. Probe 1, labeled with black heat shrink at the probe end, was in the center of the refrigerator. This bare end probe was utilized to measure the air temperature. Probe 2, with no marking, was placed into a 20-mil Boston bottle containing propylene glycol, which was also positioned at the center of the refrigerator adjacent to the air probe. Care was taken to position the glycol bottle so that it was suspended in the air, not contacting the shelf, walls or stored material.[9]

The thermistors were connected to a single Wi-Fi-enabled radio utilizing standard 802.11N communication protocol. The radio was programmed to communicate via the client's Wi-Fi network and connected to the Internet. The encrypted data were transmitted to the cloud via the Internet where they were stored on cloud servers.

The probe tip was inserted into the glycol solution in the glycol bottle and suspended in the air, ensuring that the bottle was not contacting the sides or bottom of the bottle. The bottle was filled with propylene glycol, a 50-50 admixture by weight using RO (purified) water. The use of propylene glycol was suitable for this application because the admixture of 50-50 by weight resulted in a freezing point of -33°C, well below the operating range of the refrigerator unit.

The study adhered to CDC Guidelines that require verifying temperature probe's response using a digital thermometer with a total device accuracy (i.e. uncertainty) of +/- 0.5°C. The CDC also calls for probes to be validated to a National Institute of Standards and Technology (NIST) traceable standard. In this study, calibrated probes with an accuracy of +/-0.2°C within the -30 to -10°C range were used. NIST traceable verification for each probe was accomplished using an ISO/IEC 17025 / ILAC accredited laboratory.

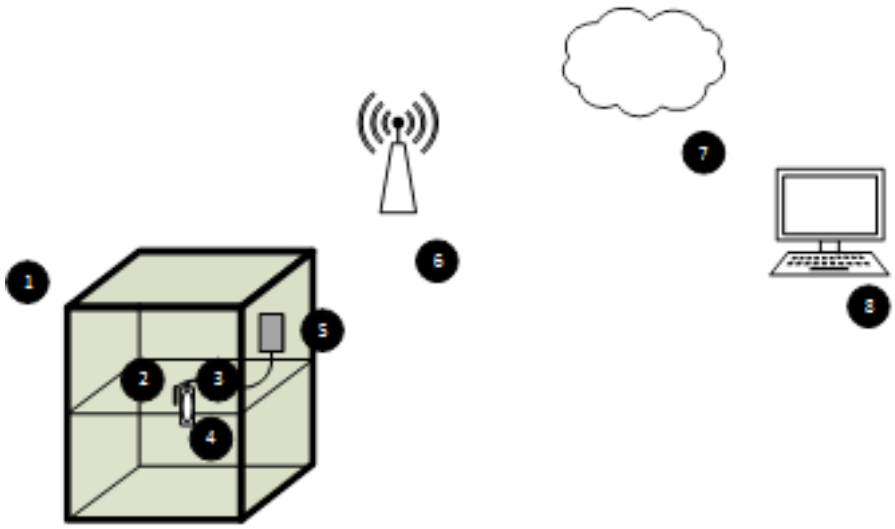
In addition to the normal steady state operation involving compressor cycles and defrost cycles, the storage unit was subjected to "open door" events that were long enough to create an air temperature well outside the specified safety range of vaccines. The duration of the "open door" events varied in typical use such as inventory selection, management, and replenishment. The temperature readings from the air temperature probe were then passed to the mathematical algorithm to compute the predicted internal temperature of the glycol bottle at the corresponding point in time.

The performance of the algorithm was evaluated on the following basis:

- Measuring the algorithm over a three-day period to determine how well it simulated the glycol temperature under a variety of normally occurring conditions one would experience in the typical use of a vaccine storage unit.
- Evaluating the repeatability and accuracy of the algorithm to predict glycol temperature.

The data ingestion, the algorithm-processing computation, and the display were accomplished via a fully validated software system compliant with all government regulations, including GMP and CFR21 Part 11.

The configuration of the major components of the data collection process is shown below in Figure 1.



1 Gem Model GAR2-S Refrigerator
2 Thermistor Probe (Air Temperature), NIST-Traceable Calibration
3 Thermistor Probe (20-ml) Glycol Temperature, NIST- Traceable Calibration
4 Glycol Bottle, 20-ml buffer, 50-50 by weight food grade glycol and RO water
5 A single Wi-Fi-enabled radio utilizing standard 802.11n communication protocol mounted external to the unit
6 Client Owned Wi-Fi and internet connection
7 Cloud Server/Database
8 Fully validated software system compliant with all government regulations, including GMP and CFR21 Part 11

Figure 1—Data Collection System

Statistical Methods

Algorithm performance was evaluated in three ways. One: the precision of the algorithm, that is, the difference in individual the raw data points received by the thermistor in the refrigerator between the algorithm and the temperature probe, was evaluated by identifying and measuring the largest differences between the two methods compared to two tolerance levels. The selected tolerance levels were 0.50°C and 0.20 °C. Two: the accuracy of the algorithm, that is, testing for potential bias, was summarized by the mean differences between predicted and measured glycol temperatures along with a 95% confidence interval. Three: the reliability of the algorithm, that is, variation in the algorithm performance over time was observed graphically with time series figures. Given that the study was conducted in a refrigerator under normal vaccine storage operation, the primary objective in terms of reliability was to determine if predictive performance varied over time, and, if so, determine the cause of lost accuracy or precision for any identified time periods of concern.[8]

Statistical analyses were conducted in Stata/IC software version 14.1. (Reference: StataCorp, College Station TX, 2015)

RESULTS

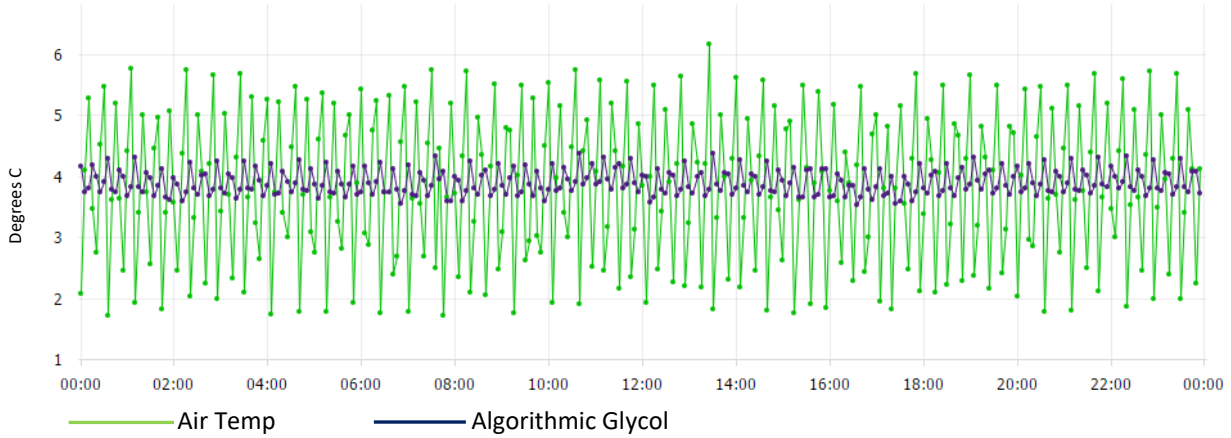


Figure 2—24-Hour Air Temperature Measurement

The data in Figure 2 show the normal operation of the refrigeration unit that was used in the test over a typical 24-hour period. Normal temperature control cycling occurred every 60 minutes and maintained an air temperature in the range of 1.7C to 6.2C.

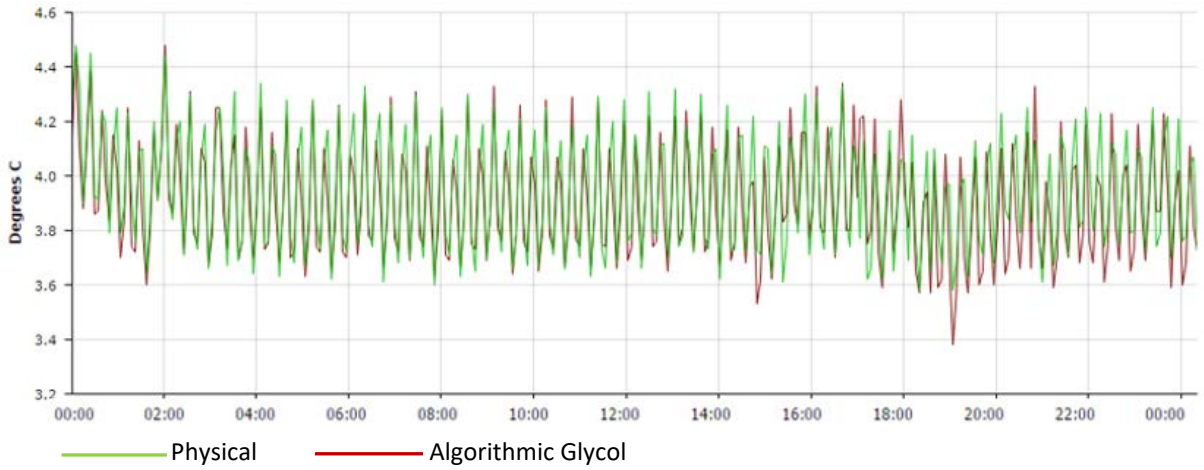


Figure 3—24-Hour Measurement of 20-ml Glycol vs Algorithmic Value

Figure 3 shows the same 24-hour period with two data streams: measured temperature from the probe inserted in the 20-ml glycol bottle and predicted glycol temperature from the algorithm for a 20-ml glycol buffer. A comparison of Figures 2 and 3 illustrates how the physical glycol dampens the air temperature variations; in Figure 2, the unbuffered air temperature ranges between 1.7 and 6.2, while in same figure the buffered temperature ranges between 3.6 and 4.3.

Figures 3 also illustrates how closely the algorithm's predictions track the physical glycol temperature. The computed value versus the actual weighted temperature returns the nearly identical values within the same sample time rate.

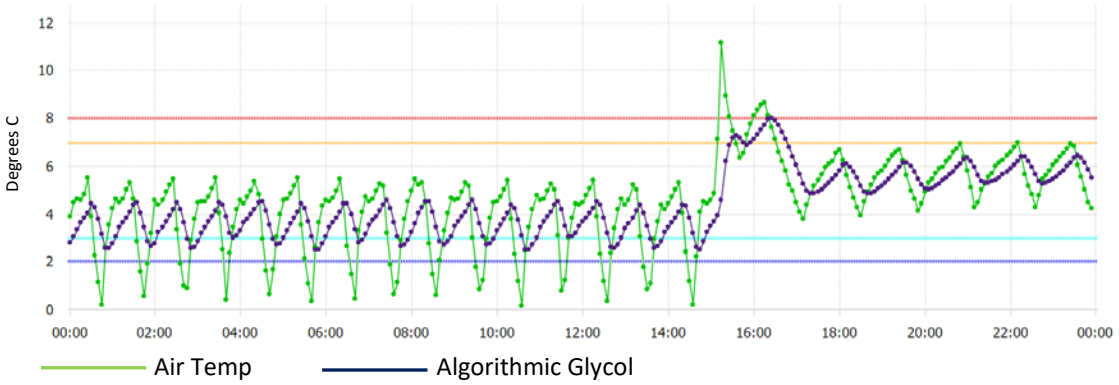


Figure 4—24-Hour Measurement of Air Temperature Excursion

Figure 4 above demonstrates the response of the algorithmic glycol's response to an air temperature excursion. When examining the response of the algorithmic glycol value, comparing the rising and falling temperatures, the algorithmic glycol tracks more readily the slowly rising temperature, while appearing not to respond to the rapidly changing cooling cycle. This is indeed the characteristic of a thermal buffer.

Precision

The algorithm demonstrated a high level of precision in predicting glycol temperature based on air temperature. Less than one-half of one percent of the differences between predicted and measured glycol were no greater than 0.20 °C (4/882) and all the raw data points received by the thermistor in the refrigerator were within 0.50 °C, which is the tolerance required by the CDC. The measurement uncertainty of the NIST validation was determined to be 0.12 C for this application.

Accuracy

The algorithm demonstrated a high level of accuracy. The mean difference between predicted and measured glycol temperature during the study was −0.078°C [95% CI −0.085 to −0.070°C]. This is evidence of a small negative bias (under prediction of measured glycol temperature), but the bias was smaller than the CDC required tolerance of 0.5 °C by nearly a factor of 10, and as such does not impact the accuracy of the temperature recordings in any meaningful way.

Discussion

The purpose of this study was to determine whether a mathematical algorithm could measure temperature comparable to the temperature within a glycol buffering container in a refrigerator. The results showed conclusively that an algorithm can accurately simulate a physically (glycol) buffered temperature measuring device. The algorithm delivers accurate,

precise readings during steady-state operation, as well as quickly reflecting changes in buffered temperatures during warming events such as defrost cycles or opening the refrigerator door (Figure 4 above).

This paper only demonstrated their equivalence for a single enclosure type—20-ml Boston bottle. This volume was selected to demonstrate the accuracy of the simulation since the smaller volume reacts more to air temperature changes, thus being the most difficult situation in which to test the algorithm. However, the algorithm, with the appropriately selected constants, can provide a predicted temperature for any desired volume. The mathematical constants that define the relationships between the buffering medium and air temperature were derived as part of this study for a variety of bottle and vial shapes and sizes.

Author's Note

The concepts demonstrated herein were tested over multiple types and sizes of storage units. Both refrigeration (2 to 8°C) and freezer (-45 to -15°C) conditions were tested comparing the physical buffer and the algorithm. In one case, 270 days of comparative data were collected. Correlation of the data for the extended test was comparable to those tests of shorter duration. The statistical analysis included herein was accomplished on data sets ranging from data sets including on day to 270 days.

The graphs presented within this document were presented in a 24-hour time span for clarification of the data. A graph displaying a longer duration would lose resolution. Noted earlier, this study was deployed to refrigeration / freezer units that were fully utilized and accessed regularly.

This study focused solely on the demonstration of a 20-ml physical temperature buffer in a static environment. Outside the scope of this study, the algorithmic buffer was

demonstrated to be accurate for multiple other shapes and volumes including cornea chambers, blood bags, and multiple other volumes.

As a separate effort, the algorithmic buffering concept was applied to a dynamic environment, i.e. transportation. The results were consistent with that of a physical buffer while utilizing individual the raw data points received by the thermistor in the storage container.

Conclusion

This paper demonstrates the ability to mimic the effect of a 20-ml physical temperature buffer, e.g., glycol with a mathematical algorithm for estimating the vaccine temperatures within a refrigerator. The advantages of an algorithmic buffer are that it is lower cost and more convenient to operate as well as less subject to problems of spillage or being moved to an inappropriate location in the refrigerator such as touching a wall.[10] The use of a buffer, glycol bottle or physical material can and often results in the improper placement of the sensing device. The use of an air temperature probe helps to ensure greater success in the correct and accurate placement of the measurement probe. The algorithm performs commensurate and reliably in real-life situations and could be used with greater efficiency than a physical buffer while continuing to make available the raw air temperature for further analysis if needed.

The ultimate intent in temperature monitoring is to know the actual experience of the stored inventory. The recommendation to use a thermal buffer is a compromise based on practical considerations. Subsequent research will further investigate the algorithm's performance with other sizes and shapes of physical buffers as well as storage fluids with different thermal characteristics, such as actual vaccine suspensions. This paper does demonstrate that the algorithm can perform as well as current best practices, and meet the recommendations provided by the CDC.

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