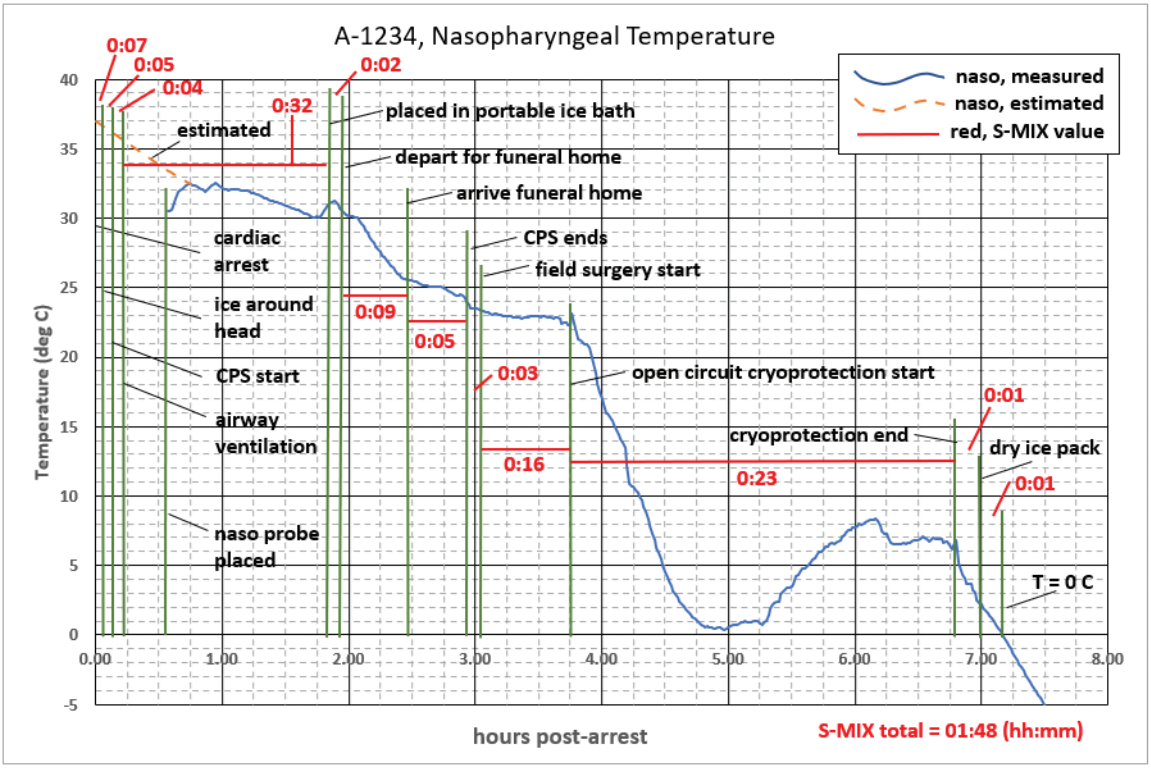
Case Report Implementation of the S-MIX (Standardized Measure of Ischemic Exposure)

By Brook Norton

For most of the time that cryonics has been practiced, it has been difficult to quantify how well each cryopreservation case was carried out. Determining success by observing patient revivals will not happen for decades. Further, patients are immersed in liquid nitrogen, and so are difficult to inspect. The situation is similar to the feedback problem that exists in the life extension field where it is impractical to try a therapy and then wait decades to see how long the subjects live. To get around this challenge for life extension trials, biological clocks are being developed to provide quick feedback for how many years of life a therapy can add. To work around the feedback challenge in cryonics, two fairly recent methods have been developed and implemented.

The first method has been to create a metric, applicable to both past and future cases, that quantifies ischemic damage (from lack of oxygen) in the interval from cardiac arrest until the patient temperature descends to 0º C. That is the S-MIX (Standardized Measure of Ischemic Exposure) metric, and its implementation in case reports will be reviewed here. The second feedback method is to perform a CT (computerized tomography) scan of the patient. This is accomplished while the patient remains immersed in liquid nitrogen. The CT scan produces an image that indicates the level of vitrification by showing the density of water ice (bad), or lack thereof (good) in the tissues scanned, especially the brain. S-MIX covers human cryopreservation procedures carried out above 0º C. CT scanning gives feedback for preservation quality of the entire cryopreservation, down to liquid nitrogen temperature. Both of these methods provide essential feedback to the team so that the effectiveness of various cryonics technologies can be evaluated and improved upon.

S-MIX is in units of time and provides an equivalent normothermic (normal body temperature) exposure time. For example, if a patient experiences circulatory arrest and remains undiscovered, at near normal body temperature, for 1 hour before cooling starts, then 1 hour is added to S-MIX. As patient temperature decreases, the rate of ischemic damage quickly decreases, and S-MIX accumulates more slowly. Every case incurs some ischemic damage since it takes some time to cool from normal body temperature down to 0º C. Theoretically, if a patient were somehow instantly cooled to 0º C after circulatory



arrest, there would be no ischemic damage and S-MIX would have the ideal value of 0 hours.

The derivation of the S-MIX formula was presented in "The S-MIX: A Measure of Ischemic Exposure" by R. Michael Perry and Aschwin de Wolf, in the 4th quarter, 2020 edition of *Cryonics* magazine. That article explains that the S-MIX derivation accounts for the common approximation that the metabolic rate is cut in half for every 10º C that the temperature drops. S-MIX can be calculated by dividing the temperature plot into segments, like cardiac arrest until ice bath cooling, CPS (cardiopulmonary support) until the start of surgery, etc. S-MIX, for each segment, depends on:

- starting and ending temperatures
- time spent in each segment
- whether CPS included ventilation (if so, S-MIX is reduced by 50% for that segment)
- whether blood washout included oxygenation (if so, S-MIX = 0 for that segment)

The above plot shows the patient body temperature for an actual case, from cardiac arrest until the temperature drops below 0º C. The red values are the S-MIX for each segment. They total to a final S-MIX of 1 hr 48 min. Comparing 1:48 equivalent ischemic time to the actual elapsed time of 7:10, from cardiac arrest to 0º C, it can be seen that quickly lowering the temperature dramatically reduces ischemic damage.

During patient standby, stabilization, and transport (SST), video and detailed records of dozens of parameters are collected. After the patient begins the cooldown to liquid nitrogen temperature, SST data is documented in a case report. The field report and other data, such as recorded communications, are consolidated into an Alcor case report. The case report is then reviewed to identify key events that affect S-MIX, shown by vertical green lines in the plot.

All potential S-MIX event times are entered into Excel. Final S-MIX events are designated with an "x" as shown in the below image snipped from the larger spreadsheet. Days-after-cardiac-arrest are calculated in the far-right column. Note that, for example, T+1 indicates the day following cardiac arrest (perhaps only minutes after cardiac arrest), not that the event occurs a full day later. A macro sorts the event table, moving "x" events to the top, in chronological order. Once an event is marked "x", its date/time is automatically used in the plot and in the S-MIX calculation.

Event name	date	time (MST)	Table_1 S-MIX	T+X days
Cardiac arrest	1/15/2023	23:30	x	T-0
ice bath, CPS, airway	1/16/2023	00:05	x	T+1
Transport patient to MOV for surgery	1/16/2023	00:35	x	T+1

Different cases may use different data loggers to record patient temperature. The raw data output can vary in date/time format, units of Fahrenheit or Celsius, and frequency of temperature readings. So, the raw data is copied into Excel where it is automatically pre-conditioned to a consistent date/time format, Celsius units, and a sampling frequency of 1/minute.

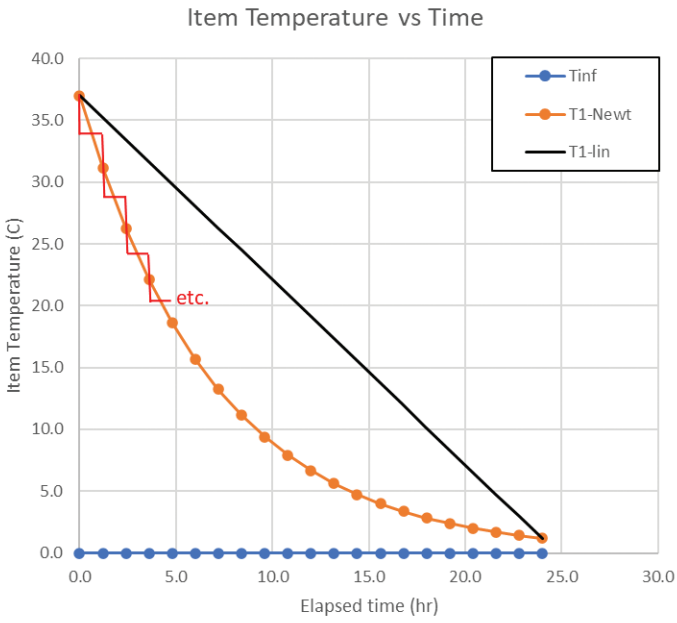
More than one datalogger stream may be used, such as for SST, transport, and cryoprotectant perfusion at Alcor. In any case, raw data is copied to Excel, concatenating datalogger streams, and covering the duration from cardiac arrest until the patient temperature passes through 0º C.

The resulting blue temperature line in the plot is reviewed for segments that may need to have corrupted data overridden, or missing data filled in with an estimate. Estimated temperatures may be needed from cardiac arrest until a temperature probe is placed, or when a probe is accidentally allowed to come in contact with ice water, or because of other possible technical glitches. Estimated data can be seen in the above plot, shown as the orange dashed line at the upper left.

Excel automatically queries the temperature data at the times designated by the green event lines. S-MIX is then calculated for the duration between every data point (typically several hundred) and summed to determine the total S-MIX.

Excel automatically plots the blue temperature line, orange estimated line(s), and green vertical event lines in the above plot. Event line labels are manually added.

The below example plot is given to illustrate how the S-MIX calculation is approached. This example shows a patient being cooled with water ice, from a normal body temperature of 37º C, down to 2º C in 24 hours. If only those two endpoints were



known, the intervening temperature decline would need to be estimated. The black line shows a linear estimate, and the orange line shows a more realistic Newtonian decline. T-infinity is the temperature that the patient would reach if allowed to cool indefinitely, in this case, approaching 0º C, shown by the blue line.

The above-mentioned article by Perry and de Wolf provides equations for calculating S-MIX-linear, S-MIX-Newtonian, rate of ischemic damage, and T-infinity, from just the two endpoints. The article also provides the equation for the Newtonian temperature decline, shown by the orange line in the below plot. Plotting the orange temperature line provides more insight as to why Newtonian cooling, which declines faster, gives a lower (good) S-MIX than an assumed linear cooling.

To calculate S-MIX for the orange Newtonian line, it is first broken into small segments, shown by orange dots. S-MIX for each small segment could be calculated from the equation that uses just the two segment endpoints. However, it turns out to be more computationally efficient in Excel to use a stepwise approach shown by the red line. The horizontal part of the red line gives the average temperature for that segment and the segment duration. The equation for (the rate of ischemic damage) X (the segment duration) gives the segment S-MIX contribution. The segment contributions can be summed to obtain the final S-MIX, for example 1 hr and 48 minutes in the above plot.

The Newtonian S-MIX is used in Excel because, compared to a linear approximation, it more accurately models the actual temperature drop for a cooling human body. At the same time that the Newtonian formulas were implemented, the capability to evaluate S-MIX for every datalogger point was also implemented. Ironically, the high density of datalogger points, and thus the small time between points, results in linear and Newtonian S-MIX that are nearly the same for those segments with datalogger temperatures. And so, the Newtonian capability is most valuable for filling in the gaps where datalogger data is missing.

The S-MIX Excel tool provides a convenient way to estimate ischemic damage for cryopreservation cases with complete, or incomplete temperature data. The detailed S-MIX mathematics are built into the tool so that case-report writers need not engage the mathematics, needing only to enter time and temperature data.

The S-MIX analysis will be presented in new case reports. The primary goal is to provide feedback on which cryonics procedures are most effective at reducing ischemic damage, pointing the way to improved procedures for future cases. ■