

A Computational Procedure for Mean Kinetic Temperature Using Unequally Spaced Data

Christopher Tong* and Amy Lock†

Abstract

The mean kinetic temperature (MKT) concept is reviewed and derived from the Arrhenius equation for the case of unequally spaced data. A new computational formula is presented for MKT using timepoint-temperature data pairs at unequally spaced time points, using a trapezoidal approximation. This formula allows the calculation of MKT for data loggers that change their sampling frequency in response to a temperature excursion or other alarm.

Key Words: Mean kinetic temperature, stability, Arrhenius equation, Trapezoidal rule

1. Introduction

The stability of pharmaceutical, biological, and food materials depends on their storage conditions, particularly temperature. During the life of a product, the temperature that it experiences is expected to vary over time. Temperature variation changes the rate of the degradation reaction that the material is subject to. The *mean kinetic temperature* (MKT) is a way to summarize the time-history of a product's temperature exposure with a single "effective" or "virtual" temperature. The following definition of mean kinetic temperature is presented by the Food and Drug Administration (2003) based on International Conference of Harmonisation (ICH) guidance:

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period.

Similarly, the United States Pharmacopeia (2012) 35, general chapter <1150> (Pharmaceutical Stability), states that

Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation.

For further background see Bailey & Medwick (1993), Grimm (1993), Kommanaboyina & Rhodes (1999), Spevacek (2005), Chow (2007), and Seevers, et al. (2009).

In this paper, we present a derivation of the theoretical equation for MKT for unequally spaced data, which is not often presented in the literature. (Most presentations are confined to equally spaced data.) This is followed by a new computational formula that can be used for timepoint-temperature data pairs. Finally, properties of the trapezoidal approximation used in the formula are discussed, and an example will be given. First, however, we review the Arrhenius equation from chemical kinetics.

*Center for Veterinary Biologics, U.S. Department of Agriculture, 1920 Dayton Avenue, Ames, Iowa 50010; Christopher.H.Tong@aphis.usda.gov; Corresponding author.

†Center for Veterinary Biologics, U.S. Department of Agriculture, 1920 Dayton Avenue, Ames, Iowa 50010; Amy.B.Lock@aphis.usda.gov; Presenting author.

2. The Arrhenius equation

An empirical finding is that the degradation reaction often follows the *Arrhenius equation* as follows (Atkins & de Paula, 2014; Upadhyay, 2006). Let k_i denote the reaction rate constant when the absolute temperature is T_i . Then

$$k_i = Ae^{-E_a/RT_i}, \quad (1)$$

where E_a is the heat of activation of the reaction, R is the gas constant, and A is the “frequency factor,” which slowly varies with temperature. The standard value for R is 8.3144621×10^{-3} kJ/mole/degrees K (National Institute of Standards and Technology, 2010).

Although the Arrhenius equation is an empirical result that only applies to materials that behave as it describes, an expression of its form is consistent with theories of chemical kinetics (e.g., Upadhyay, 2006). For instance, A can be interpreted as the number of collisions per second, and the Boltzmann factor, e^{-E_a/RT_i} , is proportional to the probability that a given collision will result in a reaction, with E_a as the minimum energy that reactants must have in order to form products. Collision theory suggests that A varies as the square root of temperature (Atkins & de Paula, 2014); such dependence is dominated by the exponential term in Eq. (1).

The activation energy E_a must be determined experimentally, e.g., by differential scanning calorimetry, but for minor temperature excursions the MKT is remarkably insensitive to the value assumed for E_a . The United States Pharmacopeia (2012) has adopted a default value of 83.144 kJ/mole for E_a (“unless more accurate information is available from experimental studies”), since this value is representative of the range of values for common organic reactions (Grimm, 1993), and since it also simplifies the calculation: $E_a/R = 10,000$ degrees K.

3. Derivation of the theoretical equation

The MKT was first introduced by Haynes (1971) but we will present a more transparent derivation following Spevacek (2005). Suppose that the temperature exposure of a material is measured over a set of n time intervals, τ_i , for $i = 1, 2, \dots, n$, with measured temperatures T_i . Here, τ_i is a time interval (duration), not a time point. Suppose further that the relevant degradation reaction for the material follows the Arrhenius equation (1), and that the dependence of the prefactor A on temperature is negligible.

Then the extent of the degradation reaction during each time interval is given by

$$\xi_i = k_i\tau_i = A\tau_i e^{-E_a/RT_i}. \quad (2)$$

The total extent of degradation is the sum of the terms (2) over all time intervals. We then define the total amount of time \mathcal{T} being monitored as

$$\mathcal{T} = \sum_{i=1}^n \tau_i. \quad (3)$$

Next, we define an equivalent material kept at constant temperature T_{mk} that has experienced the same amount of degradation, given by

$$\xi_{equiv} = A\mathcal{T}e^{-E_a/RT_{mk}}. \quad (4)$$

We now solve the following equation for T_{mk} :

$$\xi_{equiv} = \sum_{i=1}^n \xi_i \quad (5)$$

$$A\mathcal{T}e^{-E_a/RT_{mk}} = A \sum_{i=1}^n \tau_i e^{-E_a/RT_i}. \quad (6)$$

The solution is

$$T_{mk} = \frac{-E_a}{R \log \left(\frac{1}{\mathcal{T}} \sum_{i=1}^n \tau_i e^{-E_a/RT_i} \right)}. \quad (7)$$

The logarithm is base e , and the units of T_{mk} are degrees Kelvin. Note that when all time intervals are equal, this equation reduces to the usual equation for mean kinetic temperature for equally spaced data, namely,

$$T_{mk} = \frac{-E_a}{R \log \left(\frac{1}{n} \sum_{i=1}^n e^{-E_a/RT_i} \right)}. \quad (8)$$

Using Jensen's inequality, Spevacek (2005) proved that the mean kinetic temperature is never lower than the (unweighted) arithmetic average of the temperatures T_i . His proof depends only on the convexity of the relation between k_i and T_i , not on the specific form of the Arrhenius equation.

4. A computational equation for MKT

The MKT formula, Eq. (7), is not usable in practice because commercial data loggers record *time points*, not time intervals. Typically we have a set of paired data points, (t_i, T_i) , where t_i is the time at which temperature T_i is recorded. The sampling rate can vary. For instance, consider a situation where the usual sampling rate is every half hour, but it could increase to every 5 minutes if an excursion is detected. To accommodate varying sampling rates, the denominator of Eq. (7) should be modified to use the time points rather than the time intervals.

Define

$$\theta = \frac{1}{\mathcal{T}} \sum_{i=1}^n \tau_i e^{-E_a/RT_i} \quad (9)$$

as the argument of the logarithm in Eq. (7). This quantity is an estimate of the area under the curve of the quantity being summed, divided by the total time interval. In other words, we are approximating an integral (Takouis & Labuza, 1989), and we would like to do so when given the time points t_i instead of the time intervals τ_i .

Several numerical procedures are available for this approximation. In order of increasing complexity, these include the midpoint rule, the trapezoidal rule, and Simpson's rule (e.g., Phillips, 2003). I propose that the trapezoidal rule represents a reasonable compromise between simplicity and smoothness. The trapezoidal rule is based on the area formed by a trapezoid in the first quadrant, between points a and b on the horizontal axis, and $f(a)$ and $f(b)$ sampled from a function f (see Fig. 1). Suppose that $f(b) > f(a)$. The trapezoid consists of the sum of the rectangle with area $f(a) \times (b - a)$ and a triangle with area $[f(b) - f(a)] \times (b - a)/2$. The sum of these areas simplifies to $[f(b) + f(a)] \times (b - a)/2$. A composite trapezoidal rule is established by approximating an arbitrary function of time, f , sampled at unequal times, by forming trapezoids between each time point (e.g., Chapra & Canale, 2002).

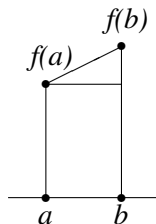


Figure 1: Trapezoidal rule illustrated.

Unlike the midpoint rule, which is a piecewise constant approximation of the temperature curve over time, the trapezoidal rule is based on a continuous interpolation “connecting the dots” between data points. The trapezoidal rule is a linear interpolation, simpler than the quadratic interpolation offered by Simpson’s rule.

A computational formula for θ is therefore:

$$\theta \approx \frac{1}{2} \times \frac{\sum_{i=1}^{n-1} (t_{i+1} - t_i) (e^{-E_a/RT_{i+1}} + e^{-E_a/RT_i})}{t_n - t_1}. \quad (10)$$

This equation uses all data pairs available. If duplicate times exist in the record, double-counting is prevented due to the subtraction $(t_{i+1} - t_i)$. Once θ is calculated, the mean kinetic temperature is simply

$$T_{mk} = \frac{-E_a}{R \log \theta}. \quad (11)$$

Equations (10) and (11) together comprise a computational algorithm for calculating the MKT with unequally spaced data. For simplicity, the relation $E_a/R \approx 10,000$ deg K may be used. Be sure to convert all temperatures to degrees Kelvin before using the equation, and convert back to original units after the calculation.

5. Properties of the trapezoidal approximation

The approximation error for a composite trapezoidal interpolant can be derived, e.g., using methods described by Phillips (2003). For the case of unequally spaced times, the result is not simple and not very useful. For the record, we present it here. There exist $n - 1$ times, ζ_i , where $t_i < \zeta_i < t_{i+1}$, such that the difference between the “true” θ and its approximated value is

$$-\frac{1}{12(t_n - t_1)} \sum_{i=1}^{n-1} (t_{i+1} - t_i)^3 \left. \frac{d^2 f}{dt^2} \right|_{t=\zeta_i}, \quad (12)$$

where $f(t) = e^{-E_a/RT(t)}$ and $T(t)$ is the unknown temperature as a function of time. This expression assumes that there is no measurement error. Let us further examine the individual terms in the above sum. When the second derivative is positive, f is convex, and the interpolant overestimates θ . Similarly when the second derivative is negative, f is concave and the interpolant underestimates θ . While the Boltzmann factor is a convex function of temperature, the temperature itself could be an arbitrarily varying function of time. Note also that if a sub-interval contains an inflection point, the error for that sub-interval may be positive or negative depending on the nature of the function and the position of sampled times that define the boundaries of the sub-interval.

There is also an “end correction” available for the composite trapezoidal rule, but it requires knowledge of the values of the first derivatives of f at the endpoints of the interval (Phillips, 2003). In practice we would not know these values.

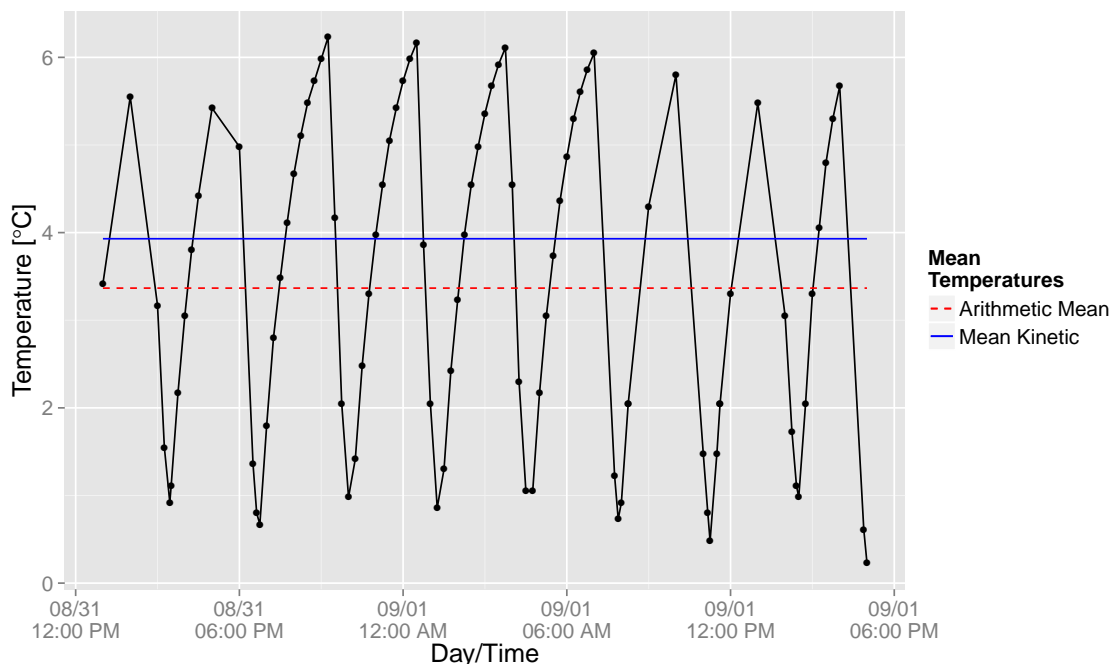


Figure 2: Temperature time series data for Aug. 31, to Sep. 1, 2011, for a refrigerator on the NCAH campus. The mean kinetic temperature (solid blue horizontal line) and, for comparison, the arithmetic mean temperature (dashed horizontal red line) are displayed.

6. An example

A temperature time series of about 28 hours, from Aug. 31, to Sep. 1, 2011, was recorded for a refrigerator at the National Centers for Animal Health (NCAH), Ames, Iowa. The data are displayed in Fig. 2, along with horizontal lines indicating the estimated mean kinetic temperature of 3.93 degrees Celsius, using Equations (10) and (11), and for comparison, the naively calculated arithmetic mean temperature of 3.37 degrees Celsius. In this example, the temperature appears to follow a cycle of warm-ups and cool-downs. The sampling frequency is usually once per every 15 minutes, but often varies from this. Intervals between readings can be as short as 3 minutes or as long as an hour.

7. Conclusions

This paper proposes a new computational procedure for calculating the mean kinetic temperature for unequally spaced data. Most of the published literature focuses on the case of equally spaced data. The new procedure allows us to calculate the MKT for situations where the temperature data logger is able to change or adapt its sampling frequency in response to excursions or other alarms.

Acknowledgments. We are grateful to John Spevacek for providing his paper, discussing these issues, and commenting on the manuscript. We thank Todd Edeker and Anna Dash for assistance with the data, and Kendall Graber, Todd Edeker, and David Siev for helpful discussions. Responsibility for any errors resides with the first author. The views expressed do not necessarily represent the views, opinions, or policies of USDA or the United States.

REFERENCES

- Atkins, P.W., and de Paula, J. (2014), *Physical Chemistry* (10th ed.), New York: W. H. Freeman.
- Bailey, L.C., and Medwick, T. (1993), "Mean kinetic temperature—a concept for storage of pharmaceuticals," *Pharmaceutical Forum*, 19 (5), 6163–6166.
- Chapra, S.C., and Canale, R.P. (2002), *Numerical Methods for Engineers, with Software and Programming Applications* (4th ed.), New York: McGraw-Hill.
- Chow, S.C. (2007), *Statistical Design and Analysis of Stability Studies*, Boca Raton, FL: Chapman & Hall/CRC.
- Food and Drug Administration (2003), *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products* (Revision 2), Rockville, MD: The United States Food and Drug Administration.
- Grimm, W. (1993), "Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products," *Drug Development and Industrial Pharmacy*, 19 (20), 2795–2830.
- Haynes, J.D. (1971), "Worldwide virtual temperatures for product stability testing," *Journal of Pharmaceutical Sciences*, 60 (6), 927–929.
- Kommanaboyina, B., and Rhodes, C.T. (1999), "Effects of temperature excursions on mean kinetic temperature and shelf life," *Drug Development and Industrial Pharmacy*, 25 (12), 1301–1306.
- National Institute of Standards and Technology (2010), *The NIST Reference on Constants and Uncertainty*, <http://physics.nist.gov/cuu/Constants/index.html>
- Phillips, G.M. (2003), *Interpolation and Approximation by Polynomials*, New York: Springer.
- Seevers, R.H., Hofer, J., Harber, P, Ulrich, D.A., and Bishara, R. (2009), "The use of mean kinetic temperature (MKT) in the handling, storage, and distribution of temperature sensitive pharmaceuticals," *American Pharmaceutical Outsourcing*, 10 (3), 30–39.
- Spevacek, J. (2005), "On the meaninglessness of 'average' temperature," *ANTEC Annual Technical Conference Proceedings*, 5, 119–123.
- Takouis, P.S., and Labuza, T.P. (1989), "Reliability of time-temperature indicators as food quality monitors under nonisothermal conditions," *Journal of Food Science*, 54 (4), 789–792.
- United States Pharmacopeia Convention (2012), *The United States Pharmacopeia 35 and the National Formulary 30*, Rockville, MD: The United States Pharmacopeia Convention, Inc.
- Upadhyay, S.K. (2006), *Chemical Kinetics and Reaction Dynamics*, New York: Springer.