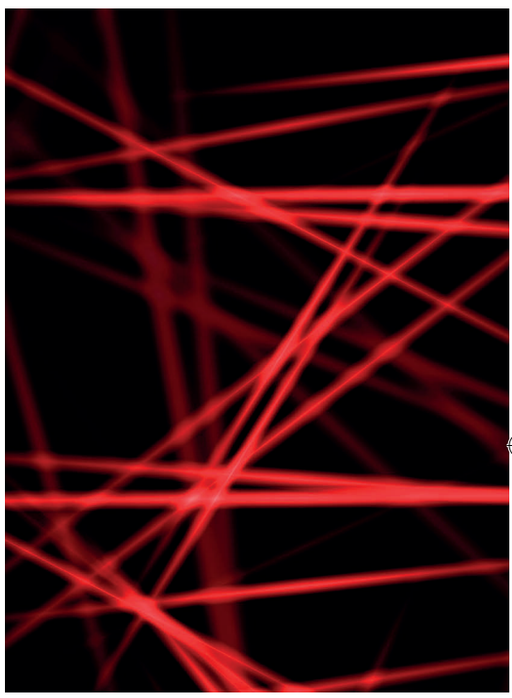
Thermal relaxation times

Target destruction while minimising damage to surrounding tissues during photothermal treatments relies on the theory of thermal relaxation. But the concept focuses on target cooling rather than destruction, write MIKE MURPHY and PER-ARNE TORSTENSSON, leading to poor results and repeat treatments



Lasers and IPLs have long been used to treat a range of unwanted blemishes on the skin. The theory of selective photothermolysis was devised in 1981 by Anderson and Parrish and was based on the pulsed laser technology of the day. This idea involved heating the target tissues without over-heating the surrounding tissue, by restricting the time in which laser energy was applied, thereby minimising collateral damage and scarring.

They applied the heat diffusion equation to a cylinder (to approximate for a blood vessel). A short energy pulse heats a cylinder then cools. Anderson and Parrish surmised that as long as the total pulse duration was less than the cylinder's "relaxation time", then no significant damage to adjacent tissues would occur outside the vessel.

By careful choice of wavelength and fluence, the selected targets could be successfully targeted and selectively destroyed. A major part of this theory was the concept of thermal relaxation time (TRT).

This is defined as the time taken "for the central temperature of a Gaussian temperature distribution with a width equal to the target's diameter to decrease by 50%". TRT is calculated, in cylinders as a first approximation, as the following; where d is the target diameter (in mm) and α is the tissue diffusivity (mm²/s):

$$\mathbf{TRT = d^2 / 16\,\alpha}$$

This definition describes the cooling time of the target. It is only dependent on the size of that target and the local heat conduction properties. By choosing pulse durations less than the TRT of the target, it was believed that a successful outcome would be produced without damaging adjacent tissues. While this is essentially true, there is a significant problem with this idea. To explain this we need to re-examine the basic physics and biology behind the light-tissue interactions.

Target destruction

The purpose of delivering light energy and, hence, generating localised heat energy in a target tissue, is to selectively destroy that target. To achieve this goal, the target must be irreversibly denatured. If the target is not damaged sufficiently, there is the probability that the tissue will simply regenerate. Consequently, the important goal is to damage the target such that it cannot regrow.

This is extremely important since it is the basis for many treatments. The TRT simply describes the target's cooling time. It has no relevance in terms of denaturing or destroying it. While the TRT may be important in minimising collateral damage, it ignores the most important task—to destroy the main target.

The key problem with this approach has been observed in poor clinical results with short-pulsed lasers and the treatment of aberrant blood vessels. Consequently, many treatment programmes were abandoned once a "plateau" in the results had been reached. Recent developments with IPL technology have improved clinical outcomes resulting from the longer pulsewidths available from these devices.

Arrhenius Damage Equation

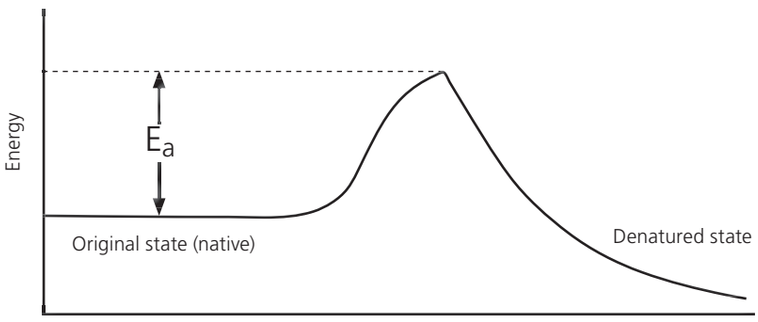
To consider how much damage a target sustains during the heating process, we need to consider the Arrhenius Damage Equation. The amount of tissue damage, Ω, at any point can be calculated as:

$$\mathbf{\Omega = A\,\delta t\,\exp(-E_a/RT)}$$

where A is the frequency of decomposition of the molecules (or damage rate factor, s^{-1}), E_a is the activation energy per mole between the native and the denatured states of tissue (J/mole), δt is the time that the energy within the target tissue is at or above the activation energy, T is the tissue temperature (in degrees Kelvin) and R is the molar gas constant (8.314 J/mole K).

This model is based on the tissue molecules absorbing an amount of energy at or above E_a followed by decomposition of the molecules at a rate determined by A. The terms E_a and A are generally known as the Arrhenius parameters.

The equation shows that the amount of tissue damage, Ω, is exponentially proportional to the temperature, T, attained by those cells and linearly with the time, δt, maintained at that temperature. Note that the time, δt, is not necessarily the same time as the pulse duration of the energy—it is the time the tissue is at, or



The activation energy required to denature tissue molecules

above, the temperature corresponding to the activation energy, or E_a.

The activation energy of any tissue differs according to the molecules in question and the denaturation pathways. This is the energy required to break molecular bonds within the tissues and is often referred to as the barrier energy.

It induces a change of state from "native" to "denatured" (see "The activation energy required to denature tissue molecules").

In essence, E_a determines the temperature at which denaturation of the tissue proteins begins, while the frequency factor, A, dictates the rate at which that denaturation occurs.

The determination of tissue damage was calculated by Diller and Pearce as the logarithm of the relative concentration of un-denatured tissue.

The level of damage may be calculated by the ratio of the concentration of native tissue, c_t, at the end of the thermal insult, at time t_1, to the concentration of native tissue prior to any denaturation, c_0, at time t_0.

Diller and Pearce showed that the logarithm of the relative concentration of undenatured collagen is the same quantity as Ω in the equation above.

The accumulated damage is defined by the dimensionless parameter Ω with the threshold for irreversible damage at a point being defined as Ω = 1. The quantity c_t / c_0 represents the proportion of undamaged tissue at the end of the applied thermal energy. This, therefore, dictates that the proportion of damaged protein may be found as follows:

$$\Omega = -\log_e(c_t / c_0) = 1$$
$$\text{i.e. } c_t / c_0 = 0.368$$

Therefore, the proportion of damaged protein, $(1 - c_t / c_0)$, is 63.2% of the initial concentration. Hence the threshold for irreversible damage, or tissue necrosis, is assumed to occur in tissue when 63.2% of the target tissue has been denatured by the thermal process.

With the definition of Ω = 1 being the threshold for irreversible protein denaturation, it is worth considering what happens when Ω is greater or less than one (see "Variation of % damaged tissue versus damage level Ω"). This shows the relationship between as Ω and the percentage of denatured proteins.

The chart below clearly shows that an Ω of one corresponds with a 63.2% damage level, while a value of three is required to achieve 95% damage. Diller and Pearce suggest that values of Ω above one are essentially meaningless since irreversibility has already been achieved in that tissue.

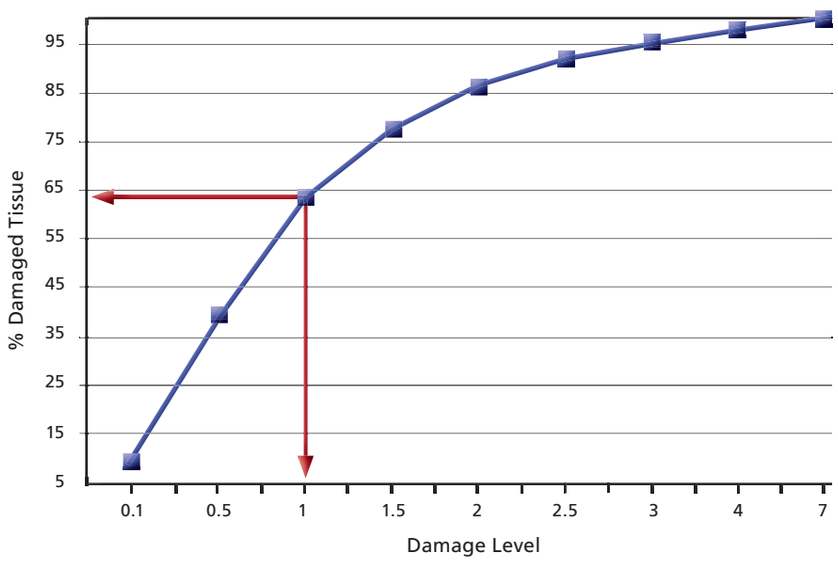
Interestingly, Takata et al suggest an Ω of 10,000 is equivalent to "third degree burns", yet calculations show that an Ω of only seven will result in 99.9% tissue damage. However, this definition is purely arbitrary. There is no clinical or histological evidence available in the literature to confirm that this assumption is accurate.

It may be that an Ω of two (equivalent to 86.5% denaturation), three (95.0%), four (98.2%) or somewhere else in that range, may actually be necessary to prevent sufficient protein re-naturation or regrowth of the existing structure occurring. We shall continue with the accepted definition of the onset of irreversible denaturation (ID) at an Ω value of one.

However, it may be that total denaturation is not required to induce the desired response. In the case of generating new collagen growth, it appears that the existing collagen merely needs to be stimulated by the application of external heat.

Our calculations reveal that the actual amount of level of damage, Ω, may be as low as only 0.1 to 0.2. Yet, even this low damage level appears to be sufficient to stimulate the fibroblasts to produce neocollagenesis.

Below: Variation of % damaged tissue versus damage level Ω



Irreversible denaturation

It is clear that the target cells must attain a temperature, T, which must be maintained for a minimum time, t, to achieve ID (Ω = 1). Consequently, it is not sufficient to simply describe a desired temperature to ensure a successful treatment outcome. The associated time for that temperature must also be indicated. The temperature-time combination is a "coupled pair"—quoting one without the other is meaningless.

So, what are the typical (T,t) combinations required to achieve ID in hair or blood vessels? These depend on the Arrhe-

	E_a	A
	(J/mole)	**(s^{-1})**
Bulk Skin	3.27×10^5	1.8×10^{51}
Blood	4.55×10^5	7.6×10^{66}

Arrhenius Parameters for bulk skin and blood (data from Diller and Pearce). The activation energy for blood is higher than that for 'bulk skin', but once it is achieved blood will denature at a much faster rate than bulk skin.

nius parameters for the tissue in question. These parameters must be found through experiment; they cannot be calculated. Many researchers have carried out such experiments for a wide range of human tissues but the data produced by Diller and Pearce will be used in this article.

The graph below shows the temperature-time combinations required to achieve ID for bulk skin and blood. The curves shows the thresholds for ID where the volume of tissue denaturation reaches 63.2% ($\Omega = 1$).

The areas above each curve therefore show all the temperature-time combinations that will induce ID for each tissue. Any temperature-time pairing which lies within those areas will exceed the damage threshold of 63.2% and render the tissue necrosed. The areas below the curves represent $\Omega < 1$ and, hence, may result in tissue re-growth.

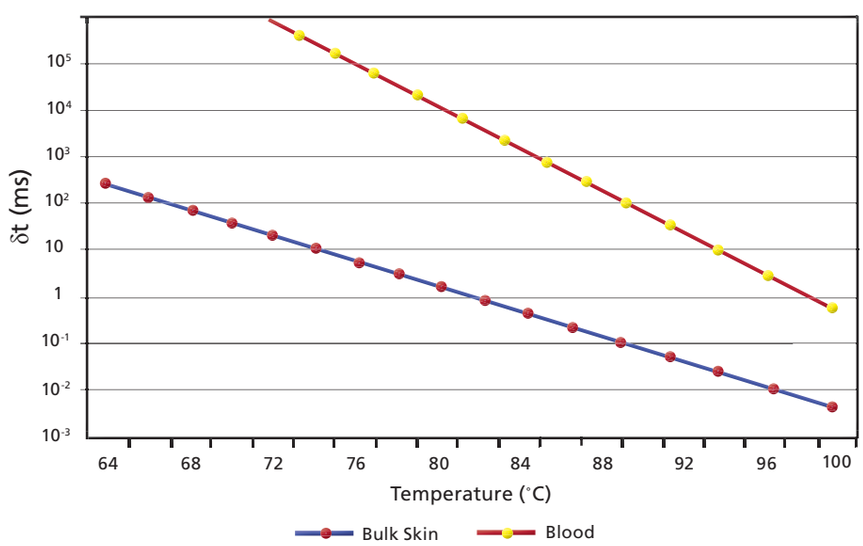
Higher temperatures require less time to induce ID compared with low temperatures. Note that the time axis in the graph below is logarithmic.

It is clear from the Arrhenius Damage Equation that the desired goal of most photothermal treatments is the attainment of irreversible denaturation. If this does not occur then tissue regrowth is possible. The time required to achieve this state is entirely dependent on the temperature achieved in the tissue. The cooling time, or TRT, is essentially irrelevant. There is no direct link between the denaturation time and the relaxation time—they describe two completely separate processes.

The Arrhenius equation shows the relationship between time and temperature. Simply achieving a desired temperature in tissue to induce a particular response is not sufficient. That temperature must be maintained for the appropriate time to achieve the desired end result. If either the temperature or the time is not attained then the response will fall short of what is clinically required, leading to poor results or excess repeat treatments.

Most importantly the equation shows that the damage achieved, Ω, due to denaturation of proteins by heat is, for any given tissue: linearly dependent on time (i.e. pulse duration); and exponentially dependent on temperature (i.e. input energy/fluence). Therefore, as long as sufficient energy has been deposited into the target then damage to the proteins can be controlled by careful selection of exposure time. Denaturation will not occur in the tissue proteins until the activation energy has been input; thereafter, a small increase in energy density (fluence) will have a major effect on the rate of the denaturation process. This strongly indicates that careful control of tissue damage is more easily achieved by judicious choice of pulsewidths, as this will result in a linear progression of denaturation.

Thresholds of irreversible damage for "bulk skin" and "blood" (Ω =1) as functions of temperature and time. The areas above each curve show the temperature-time combinations which will ensure ID. Combinations below the curves will result in less than 63.2% tissue destruction.



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