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Considering skin physiology in capacitive-coupled hyperthermia

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ABSTRACT

Dominant technical solution for oncological hyperthermia devices is capacitive-coupling. However, it has the challenge of overheating the surface of adipose layers and burning cutaneous structures. The main technical solution of this is the intensive cooling of the surface. Our objective is studying the physiology and effect of the active cooling of the skin in capacitive-coupled hyperthermia technologies.

Indexing terms/Keywords

capacitive-coupling, surface cooling, physiological reactions of skin

INTRODUCTION

Hyperthermia in oncology is an ancient method, but only modern electromagnetic methods have made its application for deep-seated tumours possible. The most effective energy-absorption in the body when we apply electric field, which could be simply realised is capacitive-coupling systems, using the radiofrequency (RF) range of electromagnetic interactions. One of the first capacitive-coupled devices was the “Universal Thermoflux”, developed by Siemens (Germany) in the first quarter of the 20th century. It was later developed into the “Radiotherm”, launched to the medical market in the early 1930s. The problem was always the proper coupling, avoiding adipose burns and surface blisters. A new capacitive technology was introduced by LeVeen [1], in 1976. This solution is widely applied since [2], [3].

There are numerous technical solutions for hyperthermia devices, most of which use some kind of capacitive-coupling. The patient in this solution is the real-load for RF-wave absorption; its impedance is serially connected to the RF-circuit (Figure 1).

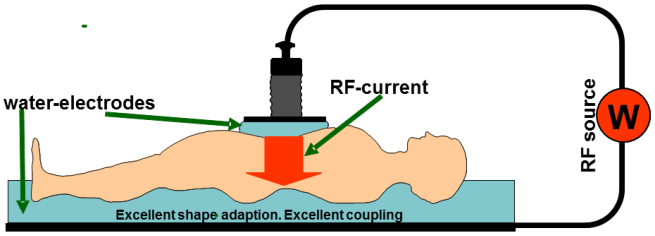

Figure 1. The patient is the serial impedance-load in the circuit, actually involving the body as part of the circuit. The solution in the figure shows an extreme size asymmetry of the electrodes, applied by oncothermia [4].

As a consequence of the advantages of simple electronics, its medical application is also simple and its control does not need special expertise. It can be used to treat all common tumours [5], [6], [7], [8], [9]. The frequency for capacitive-coupling is typically in the range of 5–30 MHz, where the standard frequencies for medical use (13.56 MHz, as well as its half and double frequencies) are preferred. Thus, many capacitive-coupled devices use 13.56 MHz for regulatory purposes.

However, the need for a large number of treatments for longer times demands better efficacy, clear dosing control and understandable feedback of the treatment for the operating conditions. Like in most technical solutions, “the devil is in the details”. It became clear that the knowledge surrounding this RF-technique alone was not enough for successful development; the system had to be refined based on physiological effects.

In addition to the technical challenges, the dosing was at the centre of the clinical applications, trying to determine the optimal needs by fixing the limits of the provided energy. The lower limit is determined by the minimal effect by heating and the upper limit is mainly determined by safety issues. For the dose consideration, we have an important point of application: the modern hyperthermia in oncology is always complementary. Consequently, studying the effect of hyperthermia alone in clinical therapies is useless; also, other methods have to be considered for hyperthermia applications. The lowest limit of the hyperthermia dose is naturally seeking normothermia, where nothing else has an action, only the complementary treatment alone. Slight heating locally or systemically probably has no direct effect on the tumour, but helps to increase the immune effects, and enhances the complementary effects by increasing blood-flow and by the exponential temperature dependence of the chemical reactions (Arrhenius law). For the upper limit, however, there are very definite technical and physiological parameters: the surface power-density of the signal is limited surface burn and the absorbed power has a limit of the hot-spots, which is a technical issue. Our objective is to investigate the physiological effects in the cutaneous layer and overcome challenges of surface toxicity.

METHOD

Capacitive-coupling uses a pair of flat electrodes, which are arranged plan-parallel, forming the capacitor. Between the electrodes, the patient represents the main dielectric matter, which the RF-current flows through. To ensure the plan-

parallelism of the electrodes, boluses are usually applied, which by its flexible formation, “smooths” the actual form of the human body, making the condenser close to ideal (Figure 2.).

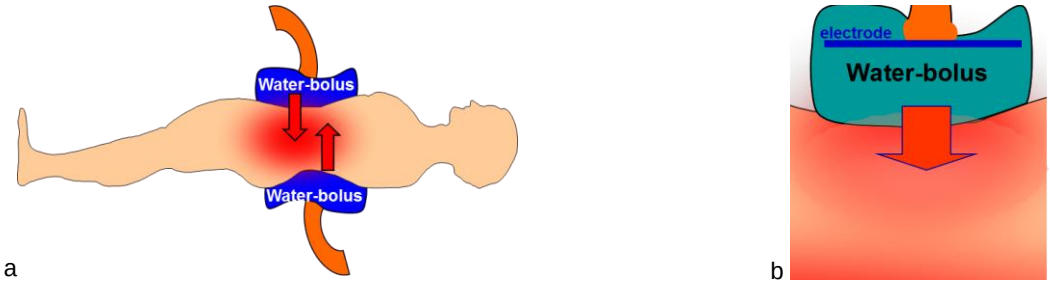

Figure 2. The flexible boluses (a) make it possible to correct the form differences between the flat capacitive electrode and the actual shape of the body (b)

The RF-source is a power-supply, fixing the desired power transmitted to the treated volume. Irrespective of wave or conductive (impedance) arrangement, the surface where the incident energy is delivered (the skin of the patient) absorbs more of the energy than the deeper layers. The energy passing through the cutaneous layers is limited by the blistering toxicity. The blistering limit depends on the density of energy (W/cm2) and the duration time of its application (Figure 3.) [10].

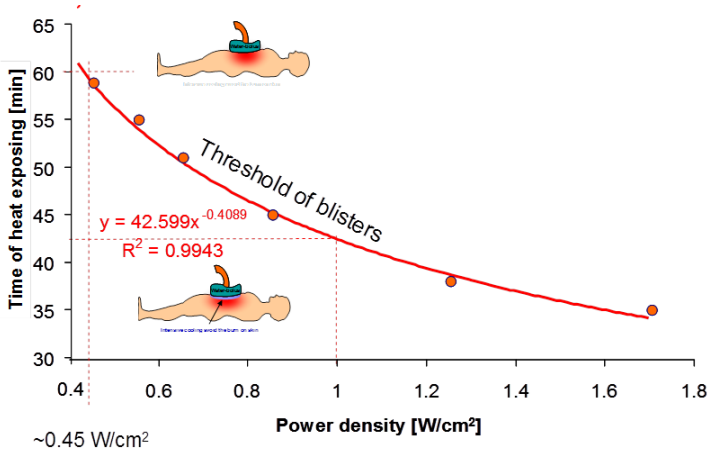

Figure 3. The blistering limit of the heating through the skin is approx. 0.5W/cm2 for a 60 minute treatment.

This could complicate the treatment, because the heat-tolerance of the skin limits the energy-load needing to be transmitted to the target. The actual threshold is very personal, but generally does not allow sufficient heat energy to the deep-seated target (Figure 4.). The actual threshold sensitivity for coupling between the skin and the electrode, as well as the structure and the physiology of the skin, are substantial factors. The thick adipose layer by its isolation behaviour makes a large jump of the electric field through the tissue, which further lowers the threshold of the tolerance of the patients.

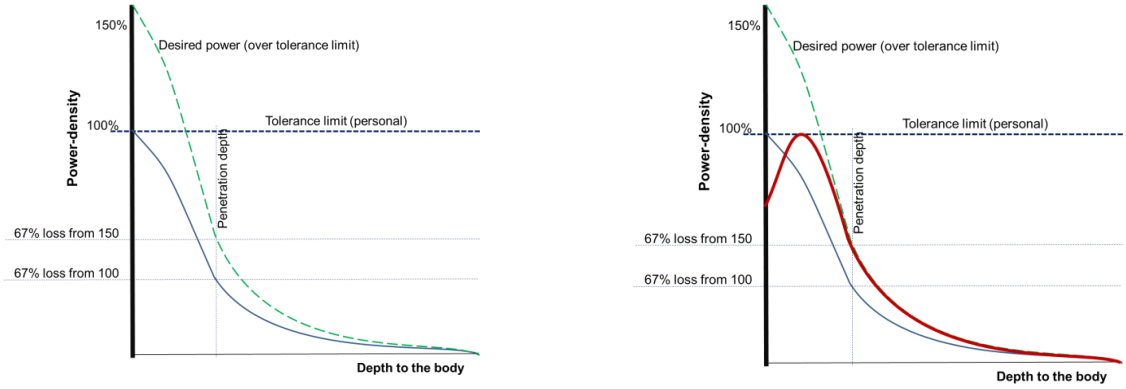

Figure 4. The energy absorption declines by depth. The penetration depth defined by the depth, where the loss is 67% of the incident energy. Due to the personal tolerance limit appropriate surface cooling is applied, and increases the penetration depth in the body. Note, the real penetration is infinite but has robust decrease of the effective specific energy by the depth.

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Modifying this threshold allows higher energy-transfer through the skin, but prevents exceeding the tolerance; intensive cooling of the form- and dielectric-correction boluses is applied in most capacitive-coupled solutions. This solves the problem of the limit of energy-transfer, and in fact unlimited huge RF-power could be applied when proper intensive cooling is used.

DISCUSSION

A race was started for robust power-supplies and the kW range of power was applied. The rivalry for the high power density in the focused area was concentrated on technical terms. However, the cooling-heating equilibrium became increasingly more instable with the higher level of energy. It increases the risk of burns and causes uncontrolled hot-spots in healthy tissue. From the thermal point of view, most of the forwarded energy is wasted by the intensive cooling (Fig. 5).

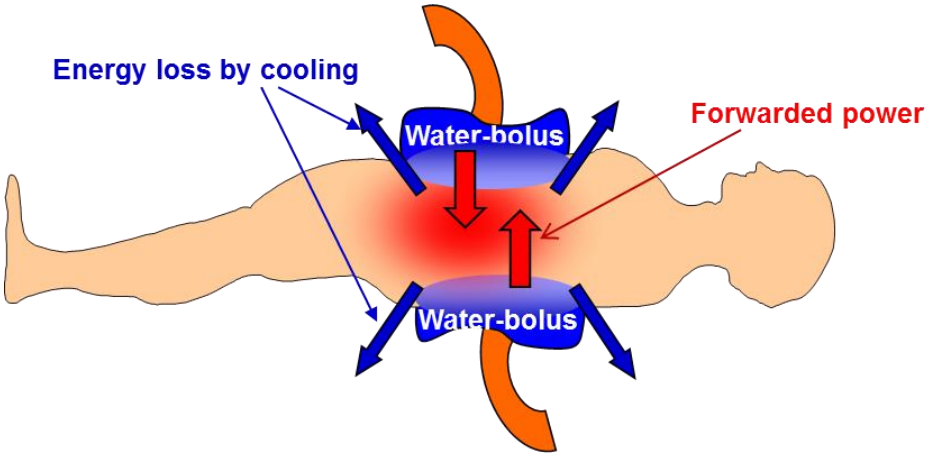

Figure 5. Intensive cooling avoids burns on the skin, but detracts an uncontrolled amount of energy. The forwarded energy could not be the dose in this situation.

This smart technical solution of surface cooling has unbeneficial characteristics in medical protocols too: due to the indefinite heat-sink of cooling, the forwarded energy cannot characterise the provided dose and something is required to measure the real absorbed energy in the target. The most plausible solution for this is measuring the temperature in the target, which could give approximate information about the absorbed heat. Unfortunately, measuring the temperature has numerous technical and physiological complications, which are discussed elsewhere [11], [12].

In the case of no-stress conditions, the temperature of the skin is also regulated by the blood-flow at heating. First, the heating is linear, like in an “adiabatic” phantom, until the reaction of the homeostatic control appears. Then, a direct vasodilatation in the heated cutaneous area starts, and a dynamic thermal equilibrium fixes the temperature higher than normothermia (Figure 6.).

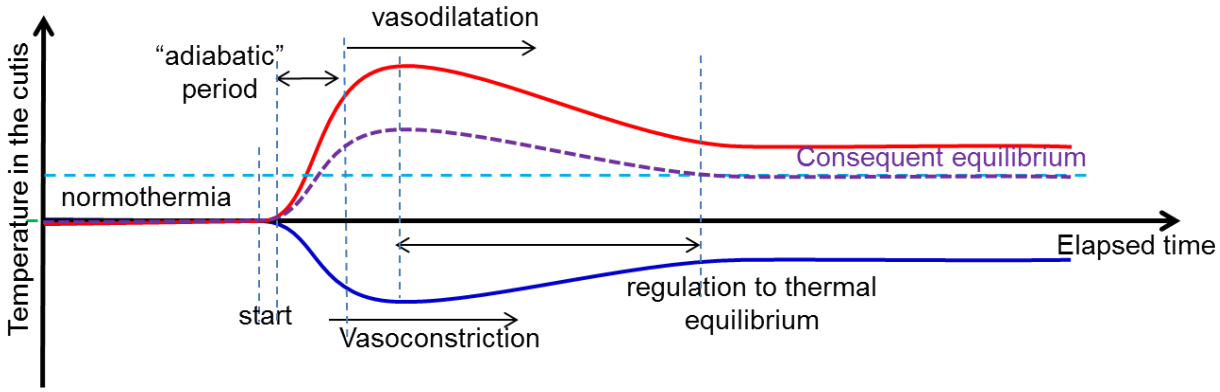

Figure 6. The physiological feedbacks balance the actual equilibrium of the surface temperature. The vasodilatation from the heating and the vasoconstriction by the cooling compete.

In the case of local heating, local homeostatic control increases the blood-perfusion. This higher blood-flow is a good heat-exchanger, spreading the locally-administered heat to the entire body; consequently, the temperature of the whole body starts to rise.

In capacitive heating technologies, the forwarded power is fixed. The vasodilatation in cutaneous volume causes higher blood-perfusion which lowers the resistivity (impedance), while vasoconstriction causes the opposite. Consequently, the radio-frequency (RF) current is actually modified by the blood-flow in the cutaneous volume (Figure 7.). Both directions of physio-regulation change the heat- and electric-conductivity of the skin.

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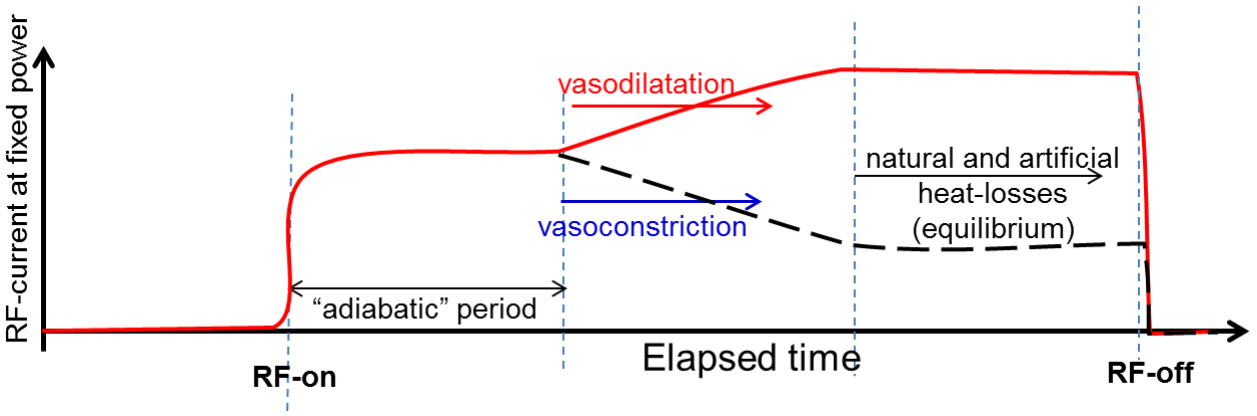

Figure 7.The actual impedance changes by the blood-perfusion state of the skin, which modifies the RF-current as well. The RF-current is the dosing value for the thermal cell-destruction in the deep-seated tumour.

In light of this impedance modification, the above challenges have additional drawbacks of intensive cooling. The skin-state is physiologically regulated to maintain local homeostatic equilibrium. The capillary-bed in the dermis is the main regulator: in a warm surface-state it increases blood-perfusion by vasodilatation, and regulates equilibrium by intensifying the heat-loss. In contrast, upon sensing a cool surface, the body downregulates the blood-flow (vasoconstriction), making isolation regulating the heat-loss effective (Figure 8.).

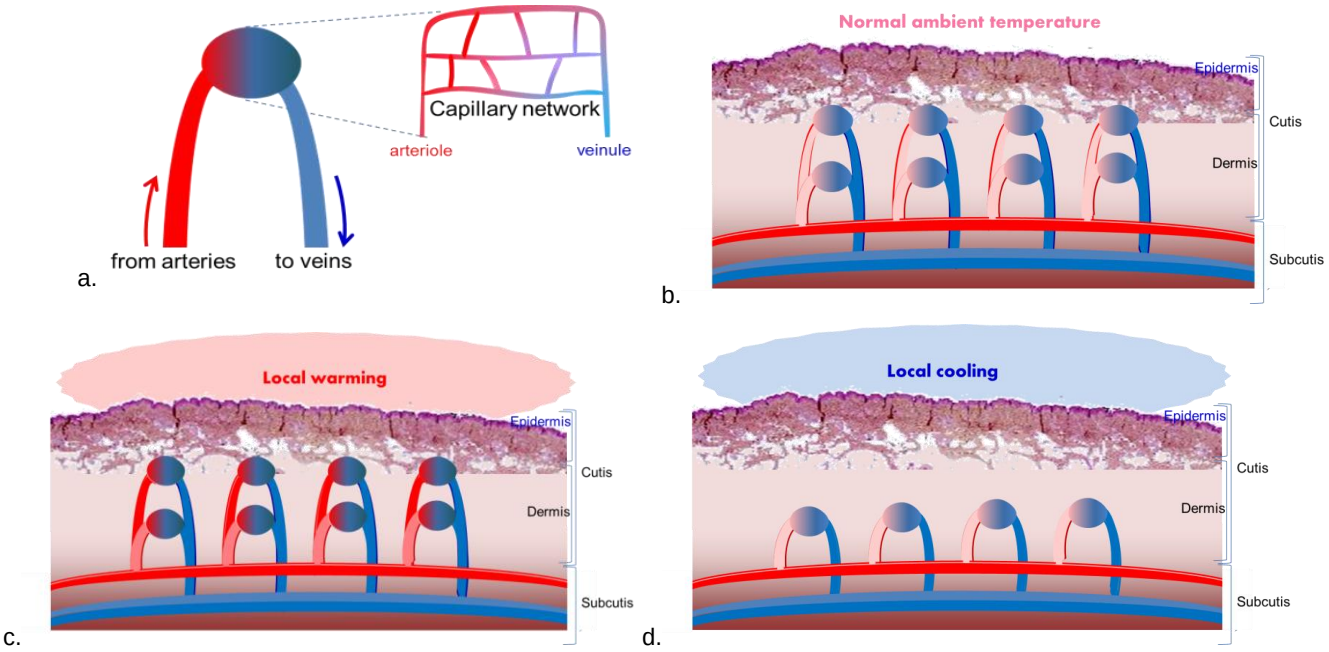

Figure 8. The cutaneous layer has a complex capillary-network (a). The normal ambient temperature balances the actual surface blood-perfusion (b). The environmental temperature significantly modifies the cutaneous blood-perfusion. The hot environment (c) stimulates vasodilatation to cool down the body, while the cold environment works oppositely (d); definite vasocontraction helps to isolate the body, and avoids the loss of body-temperature.

When the constrained forwarded power is applied, the voltage drop on the cooling-produced isolating layer will be high. Keeping the fixed power constant, high voltage is necessary to pump it through the isolating layer. The relatively high voltage lowers the RF-current. The treatment efficacy could be drastically decreased, due to the RF-current missing the deep-seated target.

On the other hand, the high surface voltage will find special conductive channels (blood-vessels, lymph passes, sweating paths, nerve-sensors, etc.) and pass through the isolating layer in a form of "sparking", causing electric burns despite intensive cooling (Figure 9.).

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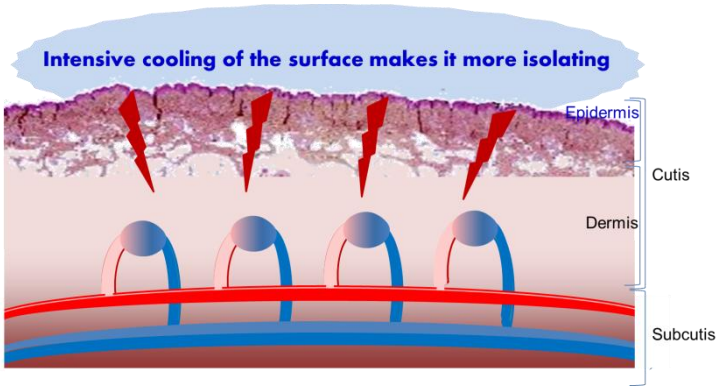

Figure 9. The constrained power produces high voltage on the skin. This causes electric burns by re-polymerisation of the proteins (see Appendix), and finds narrow channels to go through, causing a high risk of electric and thermal burns.

The large electric field value at the places of rounding with a small radius is able to ignite a polymerisation process of the surface proteins, like the temperature does at higher temperatures. In the next calculation, we show that the reaction constant of the polymerisation could be modified by electric fields, as seen for temperature (see Appendix). The thermal protein polymerisation could be trivially observed by cooking, like egg-hardening.

The rise for high-surface cooling makes a lot of drawbacks. The best solution for surface cooling is maintaining homeostatic equilibrium, which avoids the above problems [13].

APPENDIX – ELECTRIC BURNS

The stoichiometric relation of polymerisation in reaction kinetics is:

$$M_i + M = M_{i+1} \tag{1}$$

where Mi is the polymerized material containing i units of M; and so it involves the

$$\frac{d[M_{i+1}]}{dt} = k_f [M_i][M] - k_r [M_{i+1}] \tag{2}$$

reaction-kinetic equation, where the [ ] denotes concentrations, and k_f and k_r are the speed constants for the forward and reverse processes, respectively. In chemical equilibrium $\frac{d[M_{i+1}]}{dt} = 0$, and consequently:

$$\frac{k_r}{k_f} = \frac{[M_i][M]}{[M_{i+1}]} = K \tag{3}$$

We have to study K as the electric field, by deciding the direction of polymerisation.

The system is considered thermodynamically as three components:

$$dU = TdS - pdV + \\ + \mu_1 dN_1 + \mu_2 dN_2 + \mu_3 dN_3 + EdP_1 + EdP_2 + EdP_3 \tag{4}$$

where μ, P, dN are the chemical potential, polarisation and number of particles of the M_i M and M_{i+1} components denoting indexes of 1, 2, and 3, respectively, and E is the outside electric field. In the case of isobar-isotherm conditions (which are usual in these reactions), the free-enthalpy could be introduced.

$$dG = dU - TdS + pdV = \\ = \mu_1 dN_1 + \mu_2 dN_2 + \mu_3 dN_3 + EdP_1 + EdP_2 + EdP_3 \tag{5}$$

This has to be zero in equilibrium, while the condition (1) has to be fixed. Introducing the ξ reaction coordinate, the equation (1) could be eliminated:

$$dN_1 = -d\xi, \quad dN_2 = -d\xi, \quad dN_3 = d\xi \tag{6}$$

Assume the polarisation of the components proportional with the number of the particles:

$$dP_1 = p_1 dN_1 = -p_1 d\xi, dP_2 = p_2 dN_2 = -p_2 d\xi,$$
$$dP_3 = p_3 dN_3 = p_3 d\xi \tag{7}$$

Using these in equation (5), the condition of equilibrium is:

$$\mu_1 + E p_1 + \mu_2 + p_2 E - \mu_3 - p_3 E = 0 \tag{8}$$

We know (in ideal-gas approximation):

$$\mu_1 = \mu_1^0 + kT \ln[M_i], \quad \mu_2 = \mu_2^0 + kT \ln[M], \tag{9}$$
$$\mu_3 = \mu_3^0 + kT \ln[M_{i+1}]$$

(When we have liquids, we use fugacity, but this does not change the essence of the results.)

Substitute (9) into (8):

(10)

In the case of no field, the equilibrium constant is:

$$\frac{[M_i][M]}{[M_{i+1}]} = \frac{k_v}{k_e} = K = e^{-\frac{\mu_1^0 + \mu_2^0 - \mu_3^0}{kT}} = \tag{11}$$
$$= K_0(T)$$

In this case, when the outside field is zero, we know from practice that the growing temperature increases the polymerisation; therefore, the forward processes are larger than the reverse ones; k_f increases, while k_r decreases. Apply this, we get from (11):

$$\mu_1^0 + \mu_2^0 - \mu_3^0 < 0 \tag{12}$$

Similarly, using (10) in case of $p_1 + p_2 - p_3 < 0$, we see that the field has the same effect as temperature.

CONCLUSION

Hyperthermia in clinical oncology is a complementary therapy. Its physiological interaction has to be considered in all treatments. The physiological reactions of the skin are important challenges for deep-heating. The intensive cooling of the surface is a double-edged sword; it has a similar status as other medicaments: the difference between the medicine and poison is only the dose. The solution is to support homeostatic control in the cutaneous region as well [14], [15].

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