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A multiple RF heating system for experimental hyperthermia in small animals

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A versatile system is described for locally heating a number of mouse tumours simultaneously using RF capacitive coupling. The system is designed around a single RF power amplifier supplying a number of heating jigs via an efficient isolated power splitter. It is primarily intended for use at 13·56 and 27·12 MHz, but can operate from 2–30 MHz and could be modified for use at other frequencies. Microthermocouples are used for monitoring the intra-tissue temperature quasi-continuously, by making temperature measurements every 220 ms within 20 ms periods during which the RF power is turned off to all the jigs. This method avoids any artefacts in the temperature measurement which are associated with electromagnetic interference. Thermostatic regulation of tissue temperature is provided by on-off control of the average power supplied independently to each heating jig.

Key words: RF capacitive heating, hyperthermia, thermocouples.

1. Introduction

Hyperthermia is becoming widely recognized as an effective clinical tool when used in conjunction with conventional radiotherapy or cytotoxic drug therapy for malignant disease (Overgaard 1985). Significant advances have been made in our understanding of the mechanisms of action and in the application of therapeutic hyperthermia, by the use of animal models for normal tissue tolerance and tumour response to treatment (Field and Bleehen 1979, Denekamp *et al.* 1981, Hahn 1982). However, studies have been hampered by the problem of obtaining a uniform thermal dose within the treated volume. Although this is also difficult to achieve in a clinical situation, in the case of small animal models where the heated volumes are much smaller and more physically and biologically homogeneous, it is a desirable and more realistic goal.

Apart from water-bath heating, the three main techniques for non-invasive application of heat involve the deposition of electrical energy by microwaves or radiofrequency currents (RF) or the absorption of mechanical energy using ultrasonic waves. We have found that for experimental systems using small volumes of tissues, the RF methods appear to offer considerable flexibility in their operation, are simple to implement and can be extended easily to heat several animals simultaneously and independently. In this paper we present the technical description of such a system using parallel plate (capacitive) applicators in the frequency range 2–30 MHz.

2. System description

2.1. *Heating jigs and tissue power distribution*

It has been shown that selective heating of animal tumours to a high degree of temperature uniformity can be achieved using RF power capactively coupled to the tissue (Marmor *et al.* 1977, Overgaard 1978, Joiner and Vojnovic 1982). Previously developed methods of heating use matching networks to optimize the efficiency of power transfer from the power source, which generally has an output resistance equal to 50Ω, to the impedance of the tissue and electrode combination, which is usually reactive. When using applicator electrodes to couple power into the tissue care must be taken to ensure that edge effects are minimized since these cause non-uniform and unpredictable heating. This problem can be reduced by placing a bolus around the tissue (Brezovich *et al.* 1981), or by using electrodes which are large in relation to the heated volume (Hand and ter Haar 1981). In our laboratory, we use tissue-equivalent saline as a bolus material so that the electric field between the electrodes is not significantly distorted by the presence of tissue. The saline is circulated and regulated by a thermostat to control the temperature at the tissue surface while the RF currents cause heating throughout the tissue volume and determine the temperature at depth. By controlling the RF power level so that the temperature measured at depth is equal to the surface temperature, an essentially flat temperature profile may be obtained across the heated volume (Joiner and Vojnovic 1982).

A practical advantage in the use of this arrangement is that the impedance looking into the electrodes (figure 1) is largely resistive, being approximately 100 Ω for heated volumes of the order of 1 cm^3. This does not vary significantly with the electrode geometry or the presence of biological tissue for most heating applications on small animals. A disadvantage is that a poor (20–30 per cent) efficiency of power transfer to the tissue is obtained, as the saline absorbs most of the power and acts as a buffer, or isolator, between the RF source and the 'load', i.e. the tissue. However, since the heated volume rarely exceeds a few cubic centimetres in small animals, this limitation is of little practical consequence and RF powers of 5–30 W are more than ample to achieve temperatures in excess of 43°C.

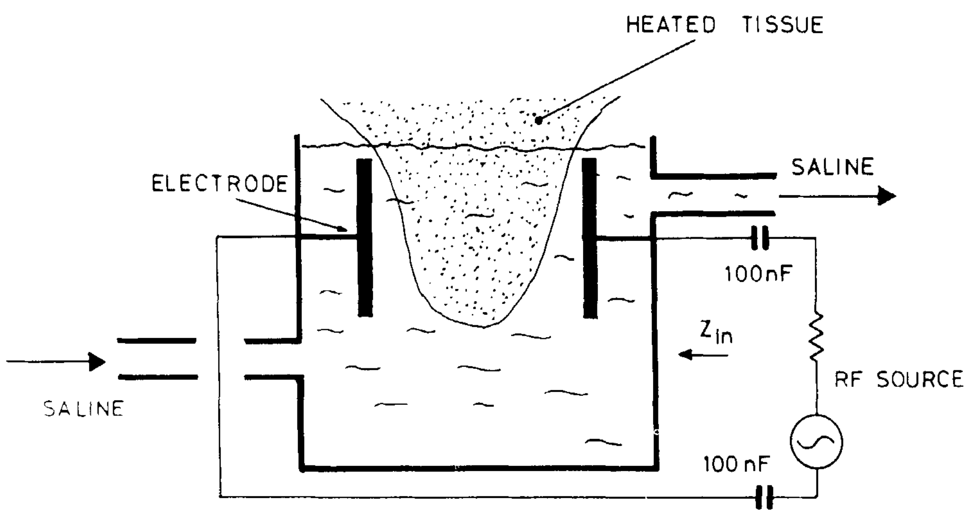


Figure 1. Outline of the heating jig used, which presents approximately a 100 Ω impedance, (Z_{in}), to the RF source. The 100 nF coupling capacitors present a negligible reactance at RF but limit mains earth loop currents set up through the RF source, the saline flow system thermostat and the mains supply.

The precise saline concentration in the liquid bolus can be adjusted so that the jig presents an impedance of 100 Ω with the tissue in place; in practice we have found it to be 0·1–0·2 per cent w/v. A detailed description of the jig, intended for heating of tumours implanted intramuscularly into mouse limbs, or subcutaneously on the chest or dorsum, has been published (Joiner and Vojnovic 1982). Similar jigs have now been developed for heating kidneys and lungs in mice.

It is a considerable advantage to be able to heat a number of animals simultaneously in order to obtain treatment data rapidly. Two approaches to providing multichannel heating are given in figure 2. In figure 2 (*a*), one low-power RF driver is used for each heating jig. In figure 2 (*b*) a single high-power driver is used and the power output divided up and coupled to each heated jig. This second method, used in the system described here, was designed to supply eight heating jigs initially with later expansion to 16 jigs. There are several advantages to this approach. Firstly, many laboratories, like ours, have only a single high-power driver available. Secondly, the RF source can easily be kept physically separate and at a distance from the interference-prone thermometry section. Finally, should the power requirements of the heating jigs change in future developments, this can be accommodated simply by replacing the low-cost splitter to cater for a decreased number

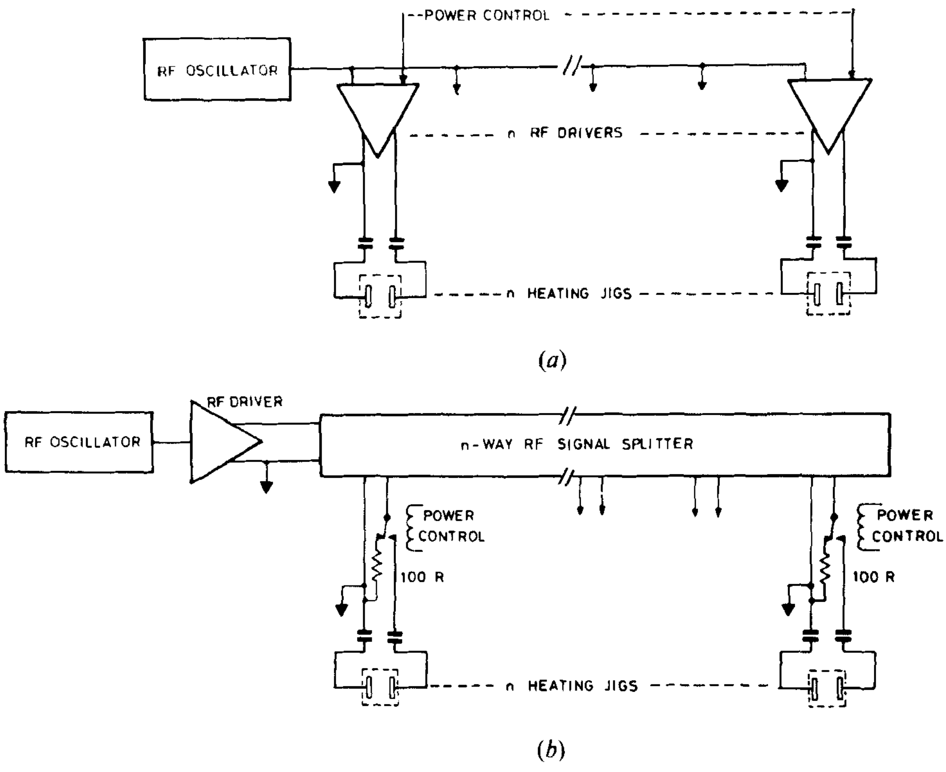


Figure 2. Simultaneous heating of a number of jigs can be performed using a number of drivers, each independently controlled as in (*a*) or by splitting the output of one driver, as in (*b*). For the latter case, the splitter output can be switched between the jig and a dummy load; the mark-space ratio of the relay operation therefore controls average power delivered to the jig.

of higher power channels, or *vice versa*. If separate drivers are used for each heating jig, these would have to be designed for the maximum expected power requirement and may be more costly than the combination of a single amplifier with a power splitter.

Independent control of RF power to each heating jig is achieved by using changeover reed relays at the outputs from the power splitter. Although not designed specifically for RF use, most reed relays, or other miniature relays, are found to be quite reliable at peak power levels below 10–20 W and at frequencies up to a few tens of megahertz. Any slight mismatch introduced by them is internally absorbed in the power splitter, as described later. The relays are used to switch RF power alternately between the jig and a 100 Ω dummy load. Average RF power fed to the jig is therefore determined by the mark-space ratio of the relay drive.

Resistive power splitters, although providing a degree of isolation between output ports, are not suitable at the power levels needed (5–10 W per channel) because of internal dissipation problems. Simple paralleling of the output channels is only adequate if the loads seen at all output ports remain equal and constant. In this application, this can never be achieved and a configuration is required with isolation between output ports. In other words, for a given input to the whole power splitter, the power level at any one of the output ports should remain largely unaffected by the load impedance presented to any of the other ports. Isolation between the single input port and the multiple output ports, although not essential, is also desirable so that a constant impedance is presented to the main power amplifier, irrespective of the loads presented to the output ports by the heating jigs. All these requirements can be met by using a hybrid junction (IRE 1955, Robinson 1961, Granberg 1975) which also has the advantage that broadband operation is simply achieved.

2.2. *The hybrid power divider*

The hybrid junction power divider, the basic building block of multi-channel power splitters, is shown in figure 3 (*a*) and one of its implementations using transmission-line transformers is shown in figure 3 (*b*). The four ports of the hybrid have the property that when power is applied to any one of the ports it is split equally and only to the two adjacent ports. In figure 3 (*a*), for example, a signal applied to the sum (Σ) port is equally present at the A and B ports, but these in-phase signals are summed in anti-phase at the difference (Δ) port to produce, ideally, zero output. In practice, this isolation between the Σ and Δ ports is deteriorated by various stray reactances caused by constructional imperfections. There is a large amount of literature on hybrid junctions, and detailed descriptions of the theory of operation and performance limitations have been published (Ruthroff 1959, Granberg 1975).

Although four ports are shown, in this instance, only three are actually used, while the fourth is terminated in its characteristic impedance. In addition, the relative phase at the splitter outputs is not important in this application as all the outputs are used independently, so both configurations in figure 3 (*c*) and 3 (*d*) are suitable. These can be used to advantage in the complete multichannel splitter as shown in figure 4, by eliminating any impedance transformation stages. Moreover, the need to have access to only one grounded port means that the final arrangement in figure 4 (*b*) is further simplified. The construction of the power splitter is

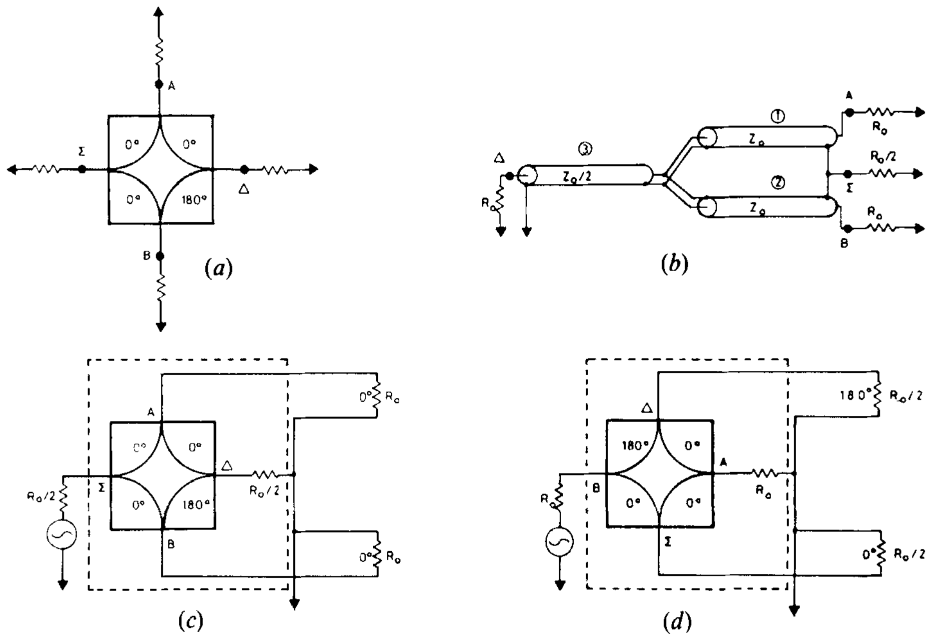
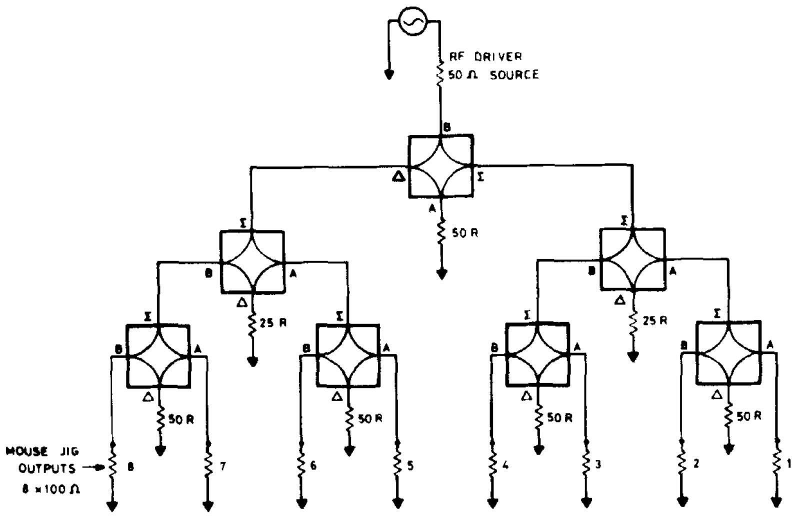


Figure 3. (*a*) The hybrid junction: signal flow between the four ports A, B, Σ, Δ can only occur along the lines shown, a phase inversion occurs between ports B and Δ, all other paths show no phase inversion. (*b*) A possible realization of the network in (*a*) using transmission line transformers; the input impedances at ports A, B are equal to the line impedance Z_0, while those at the Σ, Δ ports are equal to $Z_0/2$. For this application, the configuration in (*c*) and (*d*) can be used for power splitting to two in-phase (*c*) or out-of-phase (*d*) outputs. Any mismatch in either output is not seen by the source, but is absorbed in the internal termination, shown within dotted lines.

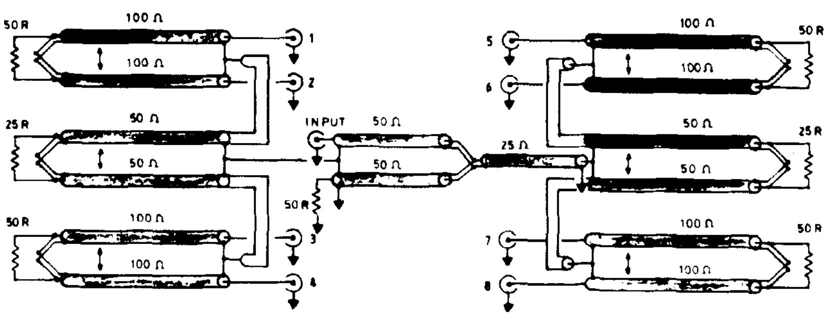
very straightforward (figure 5) and can probably be completed in less time than drawing its schematic.

It is not proposed to deal here with the theory of operation of transmission-line transformers as used in the hybrid junction. The reader is referred to papers by Ruthroff (1959), Matick (1968) and Hilbers (1967) for clear descriptions and Wiginton and Nahman (1957), Winningstad (1959) and Pitzalis and Couse (1968) for practical considerations regarding choice of core material, cable selection and winding details. It should be pointed out, however, that, unlike conventional transformers, it is primarily the transmission-line dielectric rather than the core which is involved in coupling the RF power across the transformer. For this reason, these transformers can operate efficiently at very high power levels without significant core saturation problems. In addition, it is easy to fabricate wideband devices and the 2–30 MHz bandwidth of the devices described here can be readily improved by more careful construction.

The eight-way power splitter shown in figure 4 has an input impedance of 50 Ω; a 16-way power splitter can be constructed by preceding two eight-way splitters with a two-way splitter; however, the input impedance is then either 25 Ω or 100 Ω if the described hybrid junctions are used. In either case a $\sqrt{2}$:1 voltage ratio (2:1 impedance ratio) transformer would be required for correct termination of power amplifiers with a standard 50 Ω output. It is not readily apparent that transmission-



(a)



(b)

Figure 4. (a) Eight-way matched power splitter constructed from seven hybrid junctions. The impedance at the various ports are arranged so that no mismatch occurs at the input 50 Ω; outputs, 100 Ω; or any of the internal links. Since all but one of the internal terminations are present on the Δ ports, the hybrid junction constructions are considerably simplified by omitting lines (3) in figure 3 (b). The complete transmission line implementation is shown in (b). The shaded portions of the transmission lines are wound on ferrite cores, omitted for clarity. These can be arranged so that pairs of transmission lines, linked by arrows, are wound on the same core, in opposing directions; only eight cores are thus required.

line transformers with such fractional voltage ratios can be constructed and conventional transformers are often used in this instance. The design of a transmission-line transformer which satisfies the present requirement, for all practical purposes, is presented here, and is shown in figure 6 in a version intended to make a 50 Ω to 100 Ω match. If 75 Ω cables are used, as in the prototype, the impedance ratio is strictly 50 Ω:113 Ω (72 Ω cables would produce a near-optimum 48 Ω:108 Ω). Transmission-line devices are extremely versatile and the designs

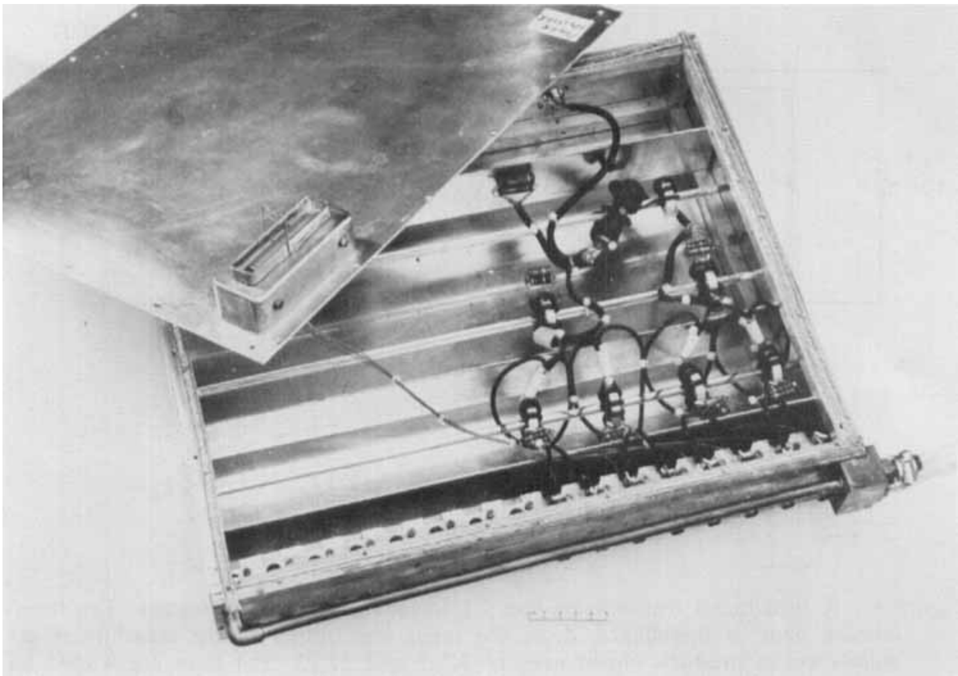


Figure 5. Photograph of the completed eight-way power splitter. The output junctions are constructed from 03074/CX cable (Gore Associates, Dunfermline, Scotland), 100 Ω, 2 × 4 turns on MM625/T1 cores (Salford Electrical Industries, Heywood, Lancashire), $\mu_r = 3000$, and RG174 cable, 50 Ω, 2 × 4 turns on MM625/T1 cores. The input junction is constructed from RG58 cables, 50 Ω, 2 × 5 turns on FX3313 (Mullard) and 2 × RG179 cable in parallel, 25 Ω, three turns on MM625/T1 cores. The power controlling relays and output loads are situated near the output connector face-plate, at the bottom of the picture. This plate can be water-cooled for high power operation (> 50 W). The isolation between outpus is typically 40 dB and does not fall below 25 dB over the range 2–30 MHz.

presented here are not unique by any means and can readily be modified to suit different frequency and power ranges or to produce power splitters with different numbers of output ports.

2.3. *The RF driver*

A block diagram of the complete RF driver unit is shown in figure 7. This consists of a purpose-built RF oscillator and exciter with an output power of 50 W which can be followed by a 200–300 W amplifier (Model C500X, RF Power Labs, Inc., Woodinville, Washington 98072, U.S.A.). All the amplifiers are within an automatic level-control feedback loop; this feature makes it possible to control the final output power using a low voltage DC control signal; any frequency–response irregularities are also smoothed out by the loop. The forward and reflected output power levels are sensed using a broadband directional coupler and rectified to provide feedback signals corresponding to the envelope of the RF signal. These are then compared with a reference signal and the resultant error signal is used to control the RF drive level through a voltage-controlled diode attenuator. The final output stages of the amplifier thus remain protected against excessive reflected power at all times and the power level can be smoothly controlled; computer

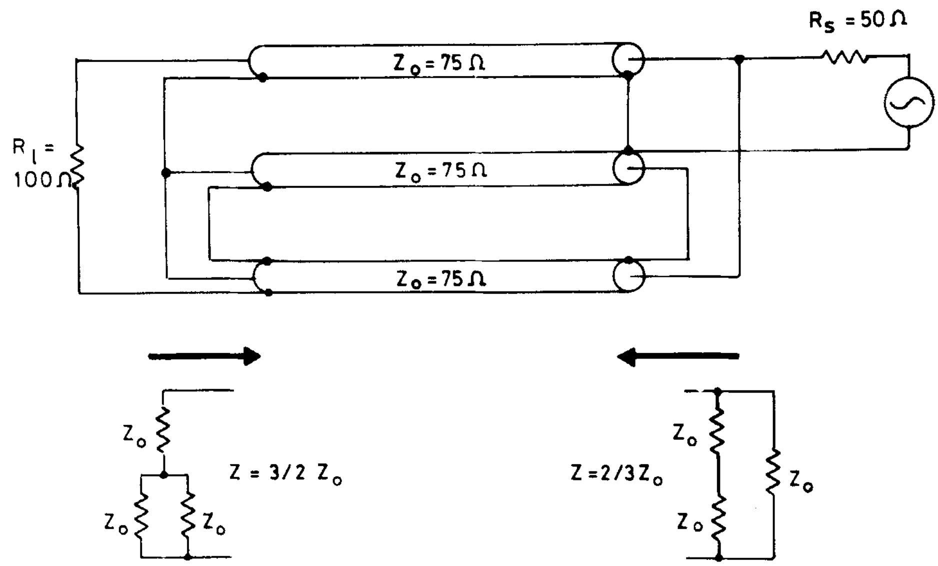


Figure 6. A broadband transmission-line 2:1 impedance ratio transformer. The transmission lines of impedance Z_0 at the input and output of the transformer are connected to produce impedances of $3Z_0/2$ and $2Z_0/3$. The lines are wound on MM625/T1 cores, 3×3 turns of RG59 cable. A bandwidth of 3–30 MHz and power handling of >200 W can be achieved.

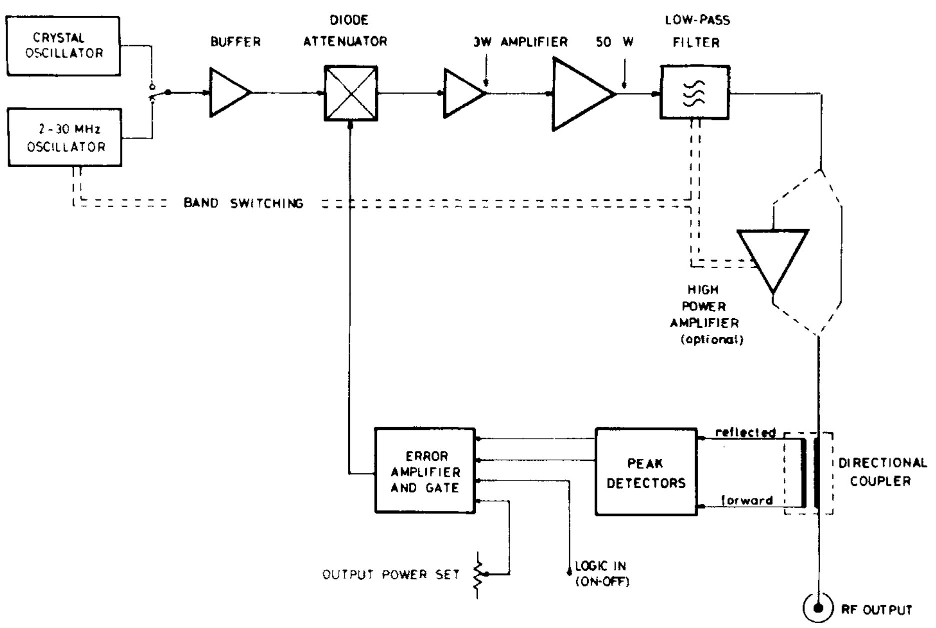


Figure 7. The RF driver system: RF generated by either a crystal oscillator (27·12 MHz) or a tunable oscillator is amplified to 50 W and can be used directly or further amplified to 200–300 W. The forward and reflected currents into a 50 Ω output load are monitored using a broadband directional coupler and the feedback loop is completed by an error amplifier and diode ring attenuator. Output power is determined by a 'power set' reference voltage; the RF can be gated off with a logic control signal. The 2–30 MHz range is covered in five approximately-octave bands.

control of output level can be easily added using a digital-to-analogue converter in the control signal path. A logic gating input is also provided which allows remote shut-down of the RF system. This feature can be used to interrupt the RF output applied to the heating jigs to allow interference-free tissue temperature measurement.

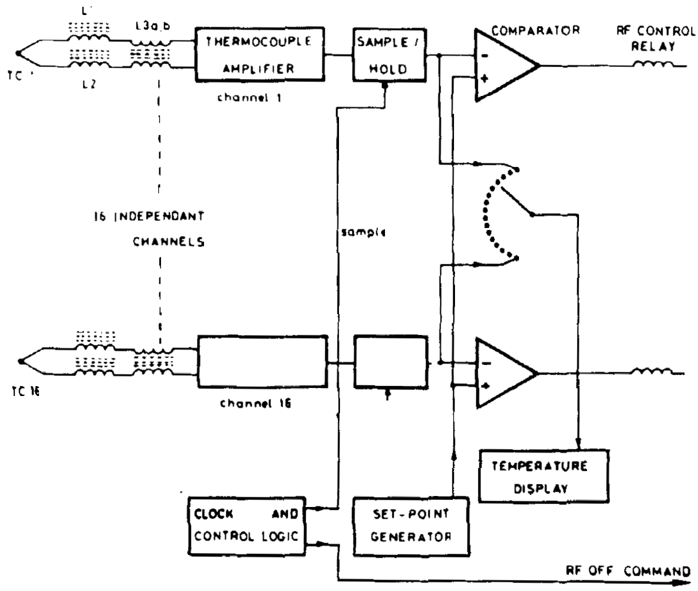
2.4. *Thermometry*

The thermometry system used in conjunction with the RF heating system is based around copper-constantan microthermocouples. The technology is not new (Grayson 1952) and recent applications have been summarized by Hand and Dickinson (1984). The thermocouples are constructed in our laboratory under a dissection microscope from 50 gauge enamelled wires, lead–tin soldered at the sensing junction and sheathed in a 0·2 mm O.D. Teflon sleeve, the end of which is sealed with polyvinyl acetate. The copper and constantan leads are maintained all the way to the signal measurement electronics. We are currently replacing the copper with manganin, as manganin–constantan thermocouples provide a more balanced input and thermal conduction errors are reduced; these advantages are discussed by Dickinson (1985).

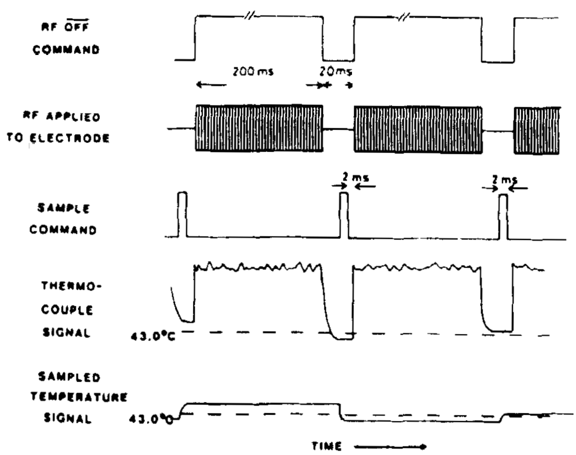
Up to 16 thermocouple signals can be processed by the system shown in figure 8. After amplification, each thermocouple signal is associated with a corresponding power control relay (figure 2 (*c*)). Each thermocouple is connected to its own individual conditioning amplifier; this arrangement was chosen in preference to a system using a single amplifier preceded by a switching or scanning unit, for several reasons. We felt that an accuracy and stability of $<0{\cdot}1\,^{\circ}C$ was necessary and this precludes the use of a fast electronic scanner unless it is within a cold-junction compensation loop. Low thermal e.m.f. relays would probably have satisfied the stability requirement but at a cost comparable to that of individual amplifiers. However their relatively low speed (10–50 ms) implies that extension beyond 8 channels would not be readily possible. Due to slight variations in the composition of thermocouple wires and connectors the absolute accuracy between different thermocouple batches is not reproducible to better than $\pm 0{\cdot}5\,^{\circ}C$ which implies that they must be calibrated individually. This is very straightforward when separate amplifiers are used. Finally, the system described here can be constructed on a modular basis and channels can be readily duplicated and their number extended.

It is essential not only to use completely electrically insulated thermocouples but also to filter their outputs, before the thermocouple amplifiers, of both common-mode and difference-mode RF interference. This prevents self-heating of the probes in the RF field and considerably reduces RF artefacts. This requirement is more important at higher frequencies, but fortunately the attenuation characteristic of most practical filters improves with frequency. The common-mode filters are made by using bifilar windings of copper and constantan wires on small ferrite toroidal cores, in effect making a 1:1 balanced-to-unbalanced transmission line transformer (Ruthroff 1959). The difference mode filters are made using windings on separate cores.

The thermocouple amplifier modules employed (type TA100, from CIL Ltd, Worthing, Sussex) include cold-junction compensation and have been found to have a short term (2 h) temperature stability of $<\pm 0{\cdot}02\,^{\circ}C$ and a long-term stability of $\pm 0{\cdot}1\,^{\circ}C$. These amplifiers provide high-level $100\,mV\,K^{-1}$ output which can be read with a digital voltmeter to give a resolution of $0{\cdot}01\,^{\circ}C$. However, rather than



(a)



(b)

Figure 8. Temperature measurement and regulation: (*a*) thermocouple signals from TC1-TC16 are filtered (L1, L2: 2×10 turns copper and constantan, 30 swg, on MM622/S1 cores, $\mu_r=750$; L3a, b: 2×10 turns copper and constantan, 30 swg, bifilar on MM622/S1 cores) and amplified to 100 mV K^{-1} by the thermocouple amplifiers. After sampling during RF periods, as shown in (*b*), the readings can be displayed on a DVM and are used to control the RF mark-space ratio through comparators and RF control relays. The set-point generator provides four preset voltages corresponding to: 41°C, 42°C, 43°C, 44°C. The clock and control logic are used to gate the RF system off, as shown in (*b*).

continuously reading the thermocouple amplifier output directly, a sample and hold circuit is used to store the temperature reading which is made during a brief interval when the RF drive is gated off. In this manner, any RF interference not adequately rejected by the copper–constantan RF filters is eliminated. We have found that a minimum RF off period of 20 ms is adequate for the TA100 amplifier. This sampling is repeated every 220 ms, giving a quasi-continuous temperature measurement and readout. This arrangement has been tested over the frequency range 2–30 MHz and power levels up to 50 W kg^{-1} tissue s.a.r. and, provided fully electrically insulated thermocouples are used, no RF-induced artefacts have been observed. The recovery of the thermocouple amplifier from the RF burst can be checked by monitoring the amplifier output on an oscilloscope (preferably of the storage variety), triggered at the start of the 'RF off' period during which the temperature is measured. A failure of the thermocouple insulation, with consequent self-heating, is then easily detected as a fast temperature change ($\tau = 100$–500 ms) as the self-heated probe equilibrates with the rest of the tissue. This change is not observed in the absence of self-heating when the thermocouple probes are undamaged.

A simple, but effective, thermostatic control system is incorporated. A comparator with a hysteresis of $<0{\cdot}05°C$ is used in each channel to compare the sampled temperature reading with a stable, manually set reference voltage (set-point). The comparator drives a corresponding RF power control relay directly. Such an on-off type of controller, with a tight control range, has been found adequate to maintain tissue temperature variations to $<\pm 0{\cdot}1°C$, as sensed by the thermocouple. In view of this level of stability, the use of more complex control loops incorporating proportional, differential or integral paths is not warranted. It is, however, desirable in this simple controller to ensure that approximately equal RF on and off periods occur for most of the heating jigs in operation, by adjusting the RF input level to the power splitter. As similar tissues will be heated in all the jigs, this is not hard to achieve.

3. Conclusion

The system described in this paper is capable of heating up to 16 animals simultaneously and independently. The RF applicator system is capable of heating tissue to a high degree of temperature uniformity and the RF power source, based around a single high-power amplifier RF followed by a series of power splitters, can be easily optimized for differing heating requirements. The power splitters described have a high degree of isolation between outputs and largely absorb any output reflections due to slight mismatches with the heating jigs so that a constant load is presented to the main RF driver. The RF output power can be adjusted simply by using a 'D.C.' control signal. The temperature regulation system is capable of maintaining the temperature at a single point in the tissue to $<\pm 0{\cdot}1°C$.

Acknowledgments

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