TUMOR TREATMENT BY TIME-REVERSAL ACOUSTICS

M. Porter, P. Roux, H. Song, and W. Kuperman

Marine Physical Laboratory
9500 Gilman Drive
La Jolla, California, 92093USA

ABSTRACT

There has been a great deal of work in ocean science over the last 10 years in using acoustic channel models in the signal processing. The goal has been to compensate for the "barbershop" effect in which a SONAR system confuses the true source with its reflections in the acoustic mirrors formed by the ocean surface and bottom. Separately, in medicine, hyperthermia has emerged as an important area of research. For hyperthermia acoustic beams are trained on tumors with the goal of reversing their growth. Our interest is the question of what (if any) lessons from the SONAR experience can be applied to hyperthermia

1. INTRODUCTION

In ocean science, model-based signal processing[22] is well established with notable experimental demonstrations. The combination of the acoustic models with the signal processing presents interesting issues. The models are challenged by the need for high accuracy; the signal processing is challenged by the need to understand and thereby exploit the reliable acoustic features.

Our interest is in the possible applications of these techniques to hyperthermia[19]. A little background … Hyperthermia is literally an increase in temperature. *Malignant hyperthermia* is the unwanted fever that can result for instance during anesthesia and lead to patient death. *Whole-body hyperthermia* is an induced fever designed to control cancer— tumor cells tend to be more sensitive to fever since their capillary system is often poorly structured and inefficient.

Local hyperthermia can be induced in many ways. Thermocouples can be directly implanted[4] or microwaves used. (Disturbing the tumor may lead to metastasis in which the cancer cells find new homes in the body.) Acoustic waveguides[9] can also be used to deliver energy directly to the tumor. Our interest here is in ultrasonically induced hyperthermia. This seems to be the method of choice, especially for deeper tumors. For this application, sound sources in the 1 to 10 MHz regime are typically used. At 1 MHz, losses are around a dB/cm so that beams focused as deep as 15 cm are intense enough to be effective. The power cannot be increased arbitrarily without causing burns to the skin.

The beam patterns may be controlled by either acoustic lenses[14][15] or by phasing elements in an array[17][6][2]. Phased arrays have the usual advantages and disadvantages of flexibility and cost. Both linear and 2D arrays have been used. The latter are often made of nested rings. The linear arrays may use elements with a directionality perpendicular to the axis of the array to provide a focus in three-space. The projector may also be scanned mechanically or with frequency shifting[24].

These sorts of acoustic systems are also used at higher power levels to perform surgery[26], or stop bleeding[25][8]. With regard to tumors there is an interesting unresolved issue of whether to use a sufficiently high temperature to actually burn the tumor[18] or just raise its temperature. Burning has the disadvantage that viable cancer cells may be dislodged. Also, there is a greater fear of accidental damage to other tissues. However, those risks must be balanced against treatment time.

Heating to lower temperatures of just 42ºC is sufficient to cause cell death and small additional increases in temperature cause a significantly greater effect. The treatment is combined with other approaches such as chemotherapy; the combination of heat and drug appears to be much more effective than either treatment alone. Even at these lower temperatures a misdirected beam is obviously undesirable. In the bowel, for instance, that temperature is sufficient to cause perforation.

2. FORMULATION

2.1 Governing Equations

The acoustic wave equation has been applied with success to the human body:

$$\nabla p = \tfrac{1}{c^2} p_{tt}$$

$$c(T) = c_0 + \beta T \ ,$$

where p is the acoustic pressure and $c(T)$ is the sound speed which (significantly) depends on temperature, T , and which is approximated by a linear function. Interestingly, the sound speed can either increase or decrease with temperature. For instance, picking some round numbers from the literature one finds that in fat a 1 degree change in temperature increases the sound speed by about 4 m/s while in muscle the same temperature change causes a drop of the same amount. A further complication is that the fat content of some tissues such as the liver is higly variable over the course of a day.

Obviously this equation is not universally adequate. In particular, shear waves may be important in bone. This is of particular concern in treating tumors in the liver, which are under the ribs[1]. Whether this is really practical is complicated by another anomalous effect of bones— they absorb ultrasonic energy very effectively and may get much hotter than the tumor.

Attenuation is easily added to the basic wave equation; however, we note that there is also a question whether a nonlinear version of this equation may be needed for the intensities used in hyperthermia[29].

The pressure heats the tissue and a linear relation has been proposed between the intensity and the heating. Hot spots within the tissue lose their heat through conduction in relation to their spatial curvature. Heat is also carried away by blood leading to the so-called perfusion term. Thus we have,

$$\rho\sigma \frac{\partial T}{\partial t} - \kappa \Delta T = w_b c_b (T - T_{art}) + 2\alpha |p|^2,$$

where ρ is the density, σ is the specific heat capacity, κ is the thermal conductivity and T_{art} is the arterial blood temperature. This is the so-called bioheat transfer equation (BHTE) which is widely used to model the thermal evolution. Of course the manner in which blood vessels carry away heat is a complicated process. In some cases, blood vessels are concentrated in parts of a tumor. Furthermore, they may contract or dilate in response to the heat. Different approximations have been studied in Refs. [11][12]

These equations for the temperature and the pressure are coupled since the intensity feeds the temperature and the temperature disturbs the sound speed which, in turn, affects the focus of the beam.

2.2 Numerical Solution

The numerical solution is in principal straightforward but in practice expensive with three space dimensions and time. Here we seek to draw on the developments of computational ocean acoustics. The temperature evolves on a slower time scale than the acoustic pressure. Thus we de-couple the acoustic and heat equations just as ocean circulation modeling is done separately from ocean acoustic propagation using the so-called *frozen ocean* approach. (See also Ref. [16].)

In particular, we take an initial homogeneous temperature distribution and compute the acoustic beam. We assume the beam is due to a single 1.5 MHz tone and look for a steady state response at that same tone. This yields the Helmholtz equation:

$$\nabla p + k_0^2 n^2 p = 0$$

where $n = c_0 / c$ is the index of refraction defined with respect to some reference sound speed, c_0. In addition, the frequency, f, of the source has been expressed in terms of a reference wavenumber $k_0 = 2\pi f / c_0$. A one dimensional Helmholtz equation $p_{xx} + k_0^2 n^2 p = 0$ can be approximately factored as $[dp/dx + jk_0 n(x) p][dp/dx - jk_0 n(x) p] = 0$ with the individual terms in square brackets being equations that can be solved separately to yield the right and left-traveling components of the pressure field. Similarly, in 2D we factor the Helmholtz equation to obtain an equation for the right-traveling component of the pressure:

$$\frac{\partial p}{\partial x} - jk_0 \left(\sqrt{n^2 + \frac{1}{k_0^2} \frac{\partial^2}{\partial y^2}} \right) p = 0,$$

where x points along the axis of the beam. The term under the square root is a pseudo-differential operator that can be approximated by a Taylor series $\sqrt{1+x} = 1 + x/2 + \ldots$. This leads to the so-called parabolic equations[10]. Similar equations can be written in 3D or with radial symmetry about the beam.

To put the whole process together, we assume that the heating effects are confined to a small box between 70 and 130 mm as shown in Figure 1. We use the analytic solution for a beam in free space to propagate the acoustic field to the left edge of the box. We then use the parabolic equation to construct the acoustic field. It is solved by dividing out the dominant $e^{jk_0 x}$ variation of the field then using standard finite-difference approximations. The resulting acoustic field becomes the heat source in the bioheat transfer equation, which is solved for 10 seconds to obtain a new temperature distribution. That temperature distribution is then used to update the sound speed in the box and the whole process is repeated.

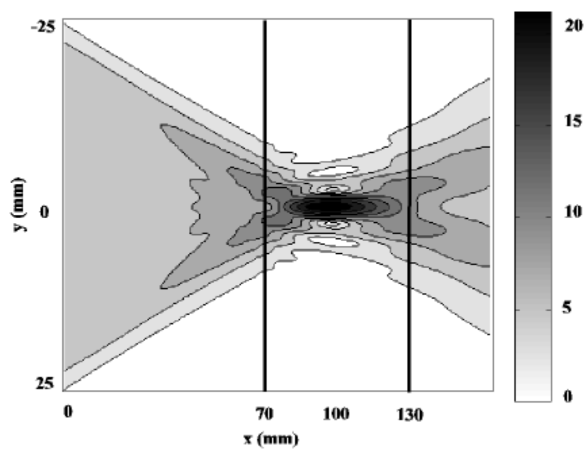

Figure 1. Configuration for the computational experiment.

3. RESULTS

3.1 Conventional Beamforming

In Figure 2 we have simulated this process for fatty tissue with a sound speed that decreases 4 m/s per degree. The beam is designed to focus at 100 mm in a homogeneous medium. Figure 2 shows the temperature elevation in degrees Celsius after 10 seconds. This is a self-focusing situation that produces well-localized heating; however, the focal spot has shifted.

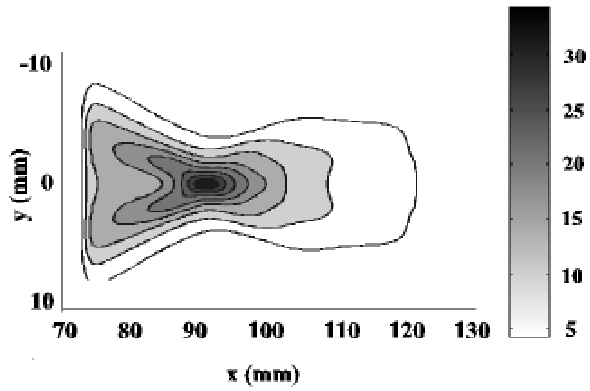

Figure 2. Temperature elevation after 10 s for a fatty tissue.

We next consider muscle tissue with a sound speed that *increases* 4 m/s for each degree rise in temperature. This leads to a warm defocusing island. As may be seen in Figure 3 the result is a much broader heated region. In addition, the focal spot has again shifted away from its intended location. Using a simpler, layered model for the sound speed a similar effect was observed in Ref.[7]. Whether this sort of error is important depends on the precise application.

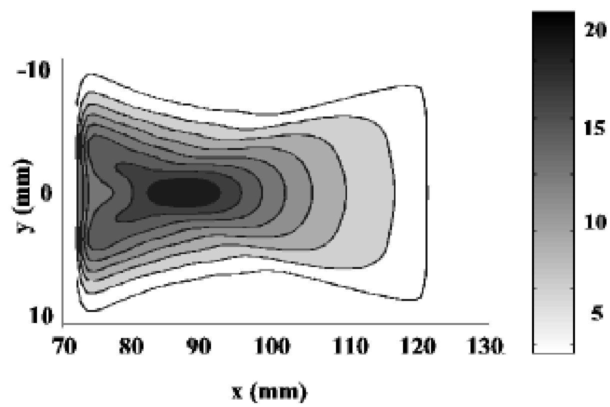

Figure 3. Temperature elevation after 10 s for muscle tissue.

3.2 Time-Reversal Focusing

The problem encountered here is analogous to that in ocean acoustics where one corrects for refraction of the acoustic beam using a model of sound propagation in the medium. In hyperthermia, an analogous approach is to solve the pattern synthesis problem to find the optimal complex weights for the phased array taking account of the medium distortion[20][5][6].

Alternatively, a simple but sub-optimal approach to this problem is to construct a phase-conjugate array or time-reversal mirror[22][13][27][27]. This can be applied to hyperthermia in two ways. We can use a computer model to predict how a hypothetical sound source at the tumor would be received on an array outside the body. Then we can time reverse that signature on the same array. This is a type of model-based beamforming that leads to a focused beam back at the tumor location. The problem with this approach is that it depends on an acoustic model of how sound propagates through a poorly known, time and space varying medium— the human body.

The second approach is to directly measure the acoustic propagation from the tumor to the treatment array. Such sources need not be loud (or large) and might be placed around the tumor rather than in it to reduce the risk of metastasis. One may also envision both electro-mechanical and chemical sound sources.

In simulation both these approaches are the same with a computer model used to propagate between the tumor and array. We have applied this approach to the defocusing case of muscle tissue. The resulting temperature field shown in Figure 4 shows that the time-reversal method provides a dramatically improved focus in terms of both sharpness and position.

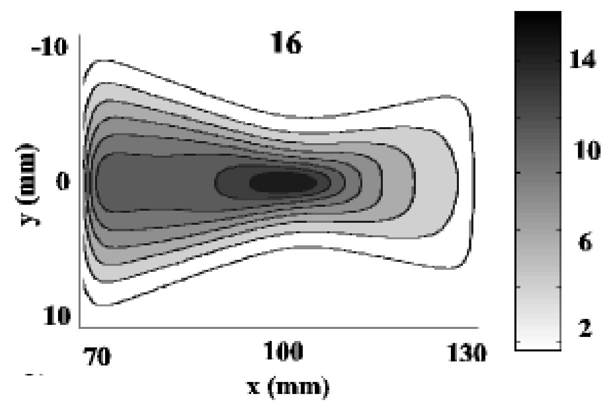

Figure 4. Temperature elevation in the treatment volume after 20 s in a fatty tissue using time-reversal focusing.

4. SUMMARY

The parabolic equation approach provides an effective tool for studying the role of spatial and temporal variations in the sound speed. We have seen that these effects lead to a shift of about 10 mm with realistically chosen values. If it is, then we have seen that the time-reversal mirror yields a simple approach to refocusing the beam at the desired location.

5. ACKNOWLEDGMENT

This work is supported by DARPA under contract number N00014-97-D-0350. M. Porter was partly supported by the New Jersey Institute of Technology sabbatical program.

6. REFERENCES

[1] Botros Y., Volakis J., VanBaren P., Ebbini E., “A hybrid computational model for ultrasound phased-array heating in presence of strongly scattering obstacles”. IEEE Trans. on Biomed. Eng., 44:1039-1050, 1997.

[2] Buchanan M. and Hynynen K., “Design and experimental evaluation of an intracavitary ultrasound phased array system for hyperthermia”. IEEE Trans. on Biomed. Eng. 41(12):1178-1187, 1994.

[3] Damianou C., Sanghvi N., Fry F., and Maass-Moreno R., “Dependence of ultrasonic attenuation and absorption in dog soft tissues on temperature and thermal dose”, J. Acoust. Soc. Am., 102 :628-634, 1997.

[4] DeFord J., Babbs C., Patel U., Fearnot N., Marchosky J., Moran C., “Accuracy and precision of computer-simulated tissue temperatures in individual human intracranial tumours treated with interstitial hyperthermia”. Int. J. Hyperthermia, 6(4):755-770, 1990.

[5] Ebbini E., Cain C., “Multiple-focus ultrasound phased-array pattern synthesis: optimal driving-signal distributions for hyperthermia”. IEEE Trans. Ultra., Ferro., and Freq. Control, 36(5):540-548, 1989.

[6] Ebbini, E. and Cain C. “Experimental evaluation of a prototype cylindrical section ultrasound hyperthermia phased-array applicator”. IEEE Trans. Ultra., Ferro., and Freq. Control, 38(5):510-520, 1991.

[7] Fan X. and Hynynen K., “The effect of wave reflection and refraction at soft tissue interfaces during ultrasound hyperthermia treatments” J. Acoust. Soc. of Amer. 91(3):1727-1736, 1992.

[8] Holt R. Cleveland R., and Roy R., “Optimal acoustic parameters for induced hyperthermia from focused ultrasound: phantom measurements with fluid flow and bubble activity”, Proceedings of the 16th Intl. Conf. on Acoustics, 1998.

[9] Jarosz B. “Feasibility of ultrasound hyperthermia with waveguide interstitial applicator”. IEEE Trans. Biomed. Eng., 43(11):1106-1115, 1996.

[10] Jensen F., Kuperman W., Porter M., Schmidt H., *Computational Ocean Acoustics*, AIP press, 1994.

[11] Kolios M., Sherar M., Worthington A. and Hunt J., “Modeling temperature gradients near large vessels in perfused tissues” in M. Ebadian and P. Oosthuizen, Eds., *Fund. of Biomed. Heat Transfer*, 295:23-30 ASME, 1994.

[12] Kolios M., Sherar M., and Hunt J., “Thermal model predictions of ultrasonic lesion formation” (1995) In L.J. Hayes, Ed., *Advances in Bioheat and Mass Transfer in Biotechnology*, 332:139-144. ASME, 1995.

[13] Kuperman W., Hodgkiss W., and Song H., “Phase conjugation in the ocean: experimental demonstration of an acoustic time-reversal mirror”, J. Acoust. Soc. Am., 103 (1), 25:40, 1998.

[14] Lalonde R, and Hunt J, “Optimizing ultrasound focus distributions for hyperthermia”. IEEE Trans. on Biomed. Eng. 42(10):981-990, 1995.

[15] Lalonde R., Worthington A., Hunt J., “Field conjugate acoustic lenses for ultrasound hyperthermia”. IEEE Trans. on Ultra., Ferro., and Freq. Control, 40(5):592-602, 1993.

[16] Le Floch C., Tanter M., and Fink M., “Self focusing and defocusing in ultrasonic hyperthermia: Experiment and simulation”. submitted to Applied Physics Letters, July 1998.

[17] Lovejoy, A., Pedrick P., Doran T., Mills J., and Stamm A., “A novel 8-bit ultrasound phased-array controller for hyperthermia applications”. Ultrasonics, 33(1):69-73, 1995.

[18] Lizzi F., “Shaping of focused ultrasound beams to expedite thermal necrosis in tumor therapy”. Proceedings of the 16th International Conference on Acoustics, 1998.

[19] Matsuda T., editor, *Cancer treatment by hyperthermia, radiation and drugs*. Taylor and Francis, London, 1993.

[20] McGough R., Ebbini E., and Cain C., “Direct computation of ultrasound phased-array driving signals from a specified temperature distribution for hyperthermia”. IEEE Trans. Biomed. Eng. 39(8):825-835, 1992.

[21] McGough R., Kessler M., Ebbini E., and Cain C., “Treatment planning for hyperthermia with ultrasound phased arrays”, IEEE Trans. Ultra., Ferro.., and Freq. Control, 43: 1074-1084, 1996.

[22] Porter M., “Acoustic Models and Sonar Systems." IEEE J. of Oceanic Engineering, OE-18(4):425–437, 1994.

[23] Seip R., VanBaren P., Cain C., and Ebbini E., “Non-invasive real-time multipoint temperature control for ultrasound phased-array treatments”, IEEE Trans. Ultra., Ferro., and Freq. Control, 43:1063-1073, 1996.

[24] Song H. and Kuperman W., “Focal translation by a frequency shift in free space,” IEEE Trans. Ultra., Ferro., Freq. Control, (in prep.) (1998).

[25] Ter Haar G., Rivens I., Rowland I., Denbow M. Fisk N. Leach M., “Occlusion of blood flow by high intensity focused ultrasound”. Proceedings of the 16th Intl. Conf. on Acoustics, 1998.

[26] Ter Haar, G., “Non-invasive ultrasonic surgery”. Proceedings of the 16th Intl. Conf. on Acoustics, 1998.

[27] Thomas J., and Fink M., “Ultrasonic beam focusing through tissue inhomogeneities with a time-reversal mirror: application to transskull therapy”, IEEE Trans. Ultra., Ferro., Freq. Control, 43:1122-1129, 1996.

[28] Wang H., Ebbini E., Cain C., “Effect of phase errors on field patterns generated by an ultrasound phased-array hyperthermia applicator”. IEEE Trans. Ultra., Ferro., and Freq. Control, 38(5):521-531 1991.

[29] Wojcik G., Mould J., Lizzi F., Abboud N., Ostromogilsky M. and Vaughan D., “Nonlinear modeling of therapeutic ultrasound”. *1995 IEEE Ultrasonics Symposium Proceedings*, pages 1617-1622.