Mathematical Methods in Emerging Modalities of Medical Imaging

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1 Overview of the Field

Computerized tomography (CT) is a major method of biomedical imaging, as well as of industrial non-destructive testing, geophysics, and other areas [20, 35, 36]. Various modalities have been developed since 1960s, including for instance the standard by now X-ray clinical "CAT scan", MRI, Optical, Ultrasound, and Electrical Impedance Tomography [25]. All of these techniques have advantages and deficiencies in terms of resolution, cost, safety, sensitivity, specificity, as well as the physiological and metabolic features they can detect. Thus a quest continues for new medical (as well as industrial) imaging modalities [25]. In recent years, a variety of novel methods have been emerging, which has lead to the need of developing the corresponding analytic and numerical tools (e.g., [3, 43–46]). The mathematics of CT has always been known for challenging and beautiful problems, and the interest of mathematicians (and surely medical professionals and engineers) in CT has been grown steadily.

The workshop assembled an impressive group of 36 mathematicians, physicists, engineers, and medical researchers, in order to assess the novel developments in CT and discuss the outstanding mathematical challenges. Among the participants there were 4 graduate students and 2 postdoctoral associates.

Among the novel techniques addressed were, for instance, elastography [26–28], electron microscope tomography [13, 40, 41], as well as several emerging so called "hybrid" modalities [1, 3, 4, 16, 21–23, 39, 43–47]. In the latter, radiation/waves of different physical nature are combined in such a way that their individual deficiencies cancel out, while advantages combine.

2 Recent Developments and Open Problems

Computed tomography, as a medical diagnostic technique, is a mature field. However, in the last decade it has experienced fast and major new developments. On one hand, the older CT modalities (X-ray CT, PET, SPECT, MRI, Ultrasound) have been going through improvements, due to technological and mathematical progress [36]. On the other hand, brand new techniques were being developed. The reasons for this advance are manifold. For instance, new physiological and metabolic parameters of biological tissues, e.g. stiffness, electrical conductivity, or hemoglobin oxygenation are attempted to be imaged. Besides, some previously addressed optical and electric parameters (e.g., optical absorption, or electric conductivity) could not be stably imaged by already existing techniques, such as Optical Tomography (OT) or Electrical Impedance Tomography (EIT). Thus, a variety of novel imaging modalities are being developed.

A variety of the so called "hybrid methods" are being introduced and studied. In such techniques, two or more types of physical waves (in most cases, ultrasound and electromagnetic) are involved, in order to overcome the individual deficiencies of each of them and to combine their strengths.

Probably the most developed, both experimentally and mathematically, among these is the so called Thermoacoustic Tomography (TAT), also known as Opto- or Photo-acoustic Tomography (PAT) [1, 5–7, 14, 15, 21–23, 29, 30, 39, 42–47]. This technique attempts to use the high contrast between cancerous and healthy tissues when irradiated by a radiofrequency electromagnetic wave or a laser beam. In TAT, a brief broad homogeneous microwave pulse irradiates the object. As the result, small portions of the EM energy are absorbed throughout the tissue. The absorption coefficient, and thus amount of energy absorbed, is known to be several times higher in cancerous areas than in the healthy ones, which leads to a wonderful contrast. However, the waves used are too long to allow for high resolution. They are used only to create energy absorption and thus minute heating of the tissues. In PAT, the same heating is achieved by irradiating by a broadened short laser pulse. However, light is also not suitable for imaging, since at the depth of several centimeters photons enter diffusion regime and the resolution is lost. Imaging in TAT/PAT is achieved by using the thermo-acoustic effect: local heating generates a propagating pressure wave, which can be detected by ultrasound transducers placed around the object of interest. These pressure measurements over a period of time allow one to recover the initial pressure distribution, directly linked to (in a crude approximation proportional to) energy absorbed. The experimental work on TAT/PAT has been going on for about 15 years, resulting in some devices industrially manufactured. However, the sorely needed mathematics of this technique has started being developed in earnest in the last 5-6 years. Major work has been done on describing the forward operator, resolving uniqueness issues, devising inversion algorithms, obtaining stability estimates and range descriptions, and considering reconstructions from incomplete data and related deterioration of images. In spite of these achievements, several important issues remain not completely resolved. One of them is recovering the actual optical properties of the tissues, rather than the initial pressure activated by heating. Another is accounting for and eliminating effect of the ultrasound attenuation. Still another is recovery of the unknown acoustic properties of the medium (in most initial studies the medium is assumed acoustically homogeneous, which might be an acceptable approximation for breast imaging, but not for imaging through a skull).

A lot of attention has been paid recently to improving methods of imaging of the internal conductivity of tissues, which provides medically important information. The standard EIT [8, 9, 11, 18] is known to suffer from intrinsic instabilities and the related low resolution [12, 31]. These deficiencies are impossible to eliminate, unless additional *apriori* information is incorporated, or the imaging process is modified. In the first case, a successful (albeit expensive) approach was recently designed that combines EIT with MR (magnetic resonance) measurements [33]. The early indications have been that incorporation of MR data stabilizes the reconstruction. However, the mathematics of this technique is rather involved and requires further development.

Another approach (or rather a variety of approaches) to stabilizing EIT is to combine it with ultrasound irradiation, which modifies the electric properties of the medium [4, 23, 29, 30, 47]. Although existence of such a (weak) electro-acoustic effect has been established [19, 24, 47], even the experimental work on this technique is in its infancy, and the mathematics (including the basic modeling) is just starting to been developed. Early indications are that the technique (called AET - electro-acoustic tomography) has a high potential for high resolution reconstruction of conductivity, which is well beyond the EIT possibilities.

Yet another approach is to notice that the currents generated in EIT trigger local heating throughout the object of interest, which in turn creates the same thermoacoustic effect that is used in TAT, and thus TAT reconstruction techniques can be used [16].

An extremely valuable Optical Tomography suffers from the same low resolution and instability ailments as EIT. An approach to OT similar to AET has been extensively studied experimentally in the last decade [43, 44, 46]. Namely, scanning the tissues with a focused ultrasound modifies locally optical properties of the tissues and thus influences the boundary optical measurements. This additional "internal" information is believed to be able to stabilize the optical tomography procedure. So far, most of the experimental set-ups work only at a shallow depth and are of the direct measurement, rather than reconstruction, type. Going deeper (a few centimeters) inside the tissue, as is needed in breast imaging, requires reconstruction techniques. The mathematics needed here is in its infancy [2, 5, 34], and even the mathematical models are being debated (as they were at this BIRS workshop).

Another recently developing medical imaging modality is elastography, which attempts to image mechanical properties (e.g., stiffness) of tissues, which are known to provide valuable medical information. Although this field is in early stages of both experimental and mathematical development, the initial experimental and mathematical studies show a high potential for medical applications.

There are manifold other novel techniques, such as for instance Electron Microscope Tomography (ET) and Cryo-Imaging, which are actively being developed for small (nano-)scale imaging of biological samples, including protein imaging. ET still faces manifold technological, and even more mathematical challenges and is being actively developed.

3 Presentation Highlights

Lectures at the workshop were given by S. Arridge (University College London), G. Bal (Columbia University), W. Bangerth (Texas A&M University), P. Burgholzer (Upper Austrian Research), S. Carney (University of Illinois Urbana-Champaign), D. Finch (Oregon State University), D. Isaacson (Rensselaer Polytechnic Institute), A. Katsevich (University of Central Florida), P. Kuchment (Texas A&M University), L. Kunyansky (University or Arizona), A. Lawrence (National Center for Microscopy and Imaging Research, UC San Diego), C. Li (Washington University, St Louis), A. Manduca (Mayo Clinic), V. A. Markel (University of Pennsylvania), J. McLaughlin (Rensselaer Polytechnic Institute), S. Moskow (Drexel University), A. I. Nachman (University of Toronto), F. Natterer (University of Münster), V. Palamodov (Tel Aviv University), E. T. Quinto (Tufts University), E. Ritman (Mayo Clinic College of Medicine), O. Scherzer (University of Vienna), J. Schotland (University of Pennsylvania), P. Stefanov (Purdue University), Y. Xu (Ryerson University, Toronto).

The presentations were, as much as possible, clustered according to the topics. Three active panel discussions were held after dinner.

We present below the outlines of the lectures.

Several talks were devoted to the actively being developed thermoacoustic/photoacoutic tomography (TAT/PAT).

A survey of main mathematical results and open problems of thermoacoustic tomography was presented in the joint talk "Can one hear the heat of a body? Survey of the mathematics of Thermo- and Photo-acoustic tomography" by D. Finch, P. Kuchment, and L. Kunyansky. Issues of mathematical modeling, uniqueness of reconstruction, inversion algorithms, stability, incomplete data problems, and others were addressed.

P. Stefanov, in a joint talk with G. Uhlmann "Thermoacoustic tomography with a variable sound speed", considered the mathematical model of thermoacoustic tomography in a medium with a variable speed for a fixed observation time interval $[0, T]$, such that all signals issued from the domain reach its boundary by time T . In case of measurements on the whole boundary, a solution in terms of a Neumann series expansion was described. Conditions close to necessary and sufficient were given for uniqueness and stability of reconstruction when the measurements are taken on a part of the boundary.

P. Burgholzer, in his talk "Image Reconstruction in Photoacoustic Tomography taking acoustic attenuation into account" addressed the important, and still not completely resolved [10, 32], issue of accounting and compensating for ultrasound attenuation in TAT. Optical detectors can provide a high bandwidth up to several 100 MHz, but the resolution is often limited by the acoustic attenuation in the sample itself, because attenuation increases with higher frequencies. Compensation for this frequency-dependent attenuation is an ill-posed problem and is limited by the thermodynamic fluctuation of the measured pressure around its mean value. These fluctuations are closely related to the dissipation caused by acoustic attenuation (fluctuation dissipation theorem) and therefore a theoretical resolution limit for the maximal compensation of photoacoustic attenuation can be estimated.

While most works on PAT are devoted to recovery of the initial pressure, which is considered the sought for tomogram, in fact the underlying optical parameters of the tissues are of interest. This barely touched problem was addressed in the talks by S. Arridge and by G. Bal.

S. Arridge, in the joint talk "Quantitative Reconstruction in PhotoAcoustic Tomography" with Ben Cox and Paul Beard, addressed the problem of quantifying the optical properties underlying the sound generation, which requires one to consider coupled models for optical and acoustic propagation. The talk presented some recent work on this problem, which utilizes a non-linear algorithm for recovering optical absorption coefficient.

The talk "Inverse transport and inverse diffusion theories for photoacoustics" by G. Bal also addressed the issue of reconstructing the optical properties from the deposited radiation, which is assumed to be obtained on the first, "standard" PAT step. It was shown what can or cannot be reconstructed in the optical parameters for two regimes of propagation of radiation: transport (joint work with A. Jollivet and V. Jugnon) and diffusion (joint work with G. Uhlmann) [6, 7].

Experimental approaches to and problems arising in PAT were considered in the Thursday presentation by C. Li (joint work with L. Wang and others).

Two talks were devoted to various versions of the recently being actively developing elastography and its medical applications.

J. McLaughlin, in her talk "Biomechanical Imaging: Viscoelastic Models, Algorithms, Reconstructions; Application to Breast, Prostate and Brain" gave an overview of the recent work of her group devoted to mathematics of bio-mechanical imaging and its applications. Biomechanical imaging was described as a promising new technology that enables monitoring of and predicting disease progression and the identification of cancerous and fibrotic tissue. The dynamic data, which was the input for the work described, were movies of propagating or harmonic waves. These movies were created from sets of MR or ultrasound data that was acquired while the tissue was moving in response to a pulse or an oscillating force. The main characteristics of these movies are: either (1) there is a wave propagating with a front; or (2) there is a traveling wave created by two sources oscillating at different but nearly the same frequencies; or (3) there is multifrequency harmonic oscillation. It was shown how data with the characteristics (1) or (2) above could be applied for cancer identification. The remaining part of the talk concentrated on the mathematical model, algorithms and reconstructions for movie data acquired when the tissue is undergoing response to a single or multifrequency harmonic oscillation. Viscoelastic and elastic models were discussed, as well as approximations to the mathematical model, with the related error estimates and algorithms. Stability and accuracy of algorithms were addressed. It was also discussed, why some biomechanical parameters cannot be reliably recovered. Images were presented that were reconstructed from synthetic, in vivo, and in vitro data.

The talk by A. Manduca "Magnetic Resonance Elastography: Overview and Open Problems" described the work on MRE done by a Mayo Clinic group. An overview of MRE and inversion techniques was presented, along with a discussion of open problems and issues. Preliminary studies indicate that MRE has substantial potential as a diagnostic tool, since it can quantitatively and non-invasively measure full $3D$ vector displacement data from propagating acoustic waves in vivo. From these data, inversion algorithms can calculate biomechanical tissue properties such as stiffness, viscosity, and anisotropy.

As it has already been mentioned, the standard Electrical Impedance Tomography (EIT) suffers from instabilities and low resolution. Several talks addressed recent attempts of creating hybrid imaging modalities that involve electrical impedance measurements as a part and aim to overcome the EIT deficiencies.

One of such modalities is the current density impedance imaging (CDI), an emerging method that combines magnetic resonance and electrical impedance measurements. Using an MR imaging device allows one to find current density inside the object to be imaged. This additional information leads to the possibility of stable reconstruction of the conductivity of the tissues. A tutorial on CDI was given by A. Nachman in his talk "Current Density Impedance Imaging", where he described the results of joint work with several mathematicians and engineers on theoretical and experimental development and implementation of this technique. It was reviewed how the current density can be determined inside an object using a Magnetic Resonance Imager (a technique invented by M.Joy's group). If two currents are available, an analytic formula for calculating the conductivity was described, and experimental validation of the method (joint work with K. Hasanov, W. Ma, and M. Joy) was demonstrated. Much of the talk addressed the problem of reconstructing the conductivity from knowledge of just the magnitude of one current in the interior (joint work with A. Tamasan and A. Timonov). The corresponding equipotential surfaces happen to be minimal surfaces in a conformal metric determined by the given data. Proof of identifiability was described and examples of numerical reconstructions given. The discovery that it suffices to measure just the magnitude of one current may lead to novel physical approaches to obtaining this data directly.

The lecture was videotaped and is available at the BIRS site
http://www.birs.ca/birspages.php?task=eventvideos&event_id=09w5017

Other hybrid techniques that allow one to overcome instabilities of the EIT were described by L. Kunyansky, O. Scherzer, and Y. Xu.

L. Kunyansky, in his joint talk "Synthetic focusing in Acousto-Electric Impedance Tomography" with P. Kuchment, discussed the so called acousto-electric tomography (AET). In AET, a focused ultrasound beam is scanned throughout the object of interest, thus modifying locally the electric conductivity, which in turn influences the boundary impedance measurements. It was shown on numerical tests that availability of this interior information stabilizes the problem of conductivity reconstruction and allows for sharp images to be recovered. A mathematical model, based on the smallness of the electro-acoustic effect, was introduced and a reconstruction algorithm discussed. Then the underlying assumption of the possibility of "perfect" focusing was addressed. Since in fact such focusing is not practical, a "synthetic focusing" approach was suggested [23] and shown to work in mathematical experiments. In this technique, a set of unfocused waves is used, and the would-be response to the impractical focused illuminations is derived mathematically.

A different way of combining electrical impedance and ultrasound measurements for ultrasound purposes was introduced by O. Scherzer (joint work with B. Gebauer) [16]. Here the starting point is that electric currents create small amount of heating throughout the object, and thus thermo-elastic expansion, similar to the one that is the basis of TAT/PAT. Then the resulting acoustic signal is picked up at the boundary and is used to recover the initial pressure and thus a tomographic image related to the unknown conductivity.

Yuan Xu delivered the lecture "Ultrasound mediated imaging methods for electrical properties of biological tissues." He described his experimental work on three different methods of combining ultrasound with electromagnetic waves for imaging purposes [29, 30, 47], as well as the underlying physics and the signal strength. The first one utilizes the changes in the ultrasound echoes from biological tissues induced by an external electrical field. The second category is devoted to detecting the electrical potential difference in biological tissues caused by applying an ultrasound field to the tissues. The third type addresses detection of the ultrasound waves emitted by biological tissues, caused by applying an electrical field to the tissues.

Yet another hybrid method under discussion, Acousto-Optical, also called Ultrasound Modulated Optical Tomography (AOT or UOT), involves a combination of optical tomography (OT) with ultrasound illumination. Here the body is irradiated by a laser beam, and the outgoing optical signals are measured at the boundary. Since the aim is to image objects of several centimeters size, one deals with multiple scattering of photons, and thus the diffusion approximation is appropriate. Simultaneous scanning with focused or unfocused ultrasound produces small, but measurable responses in the boundary measurements, which are used to reconstruct the unknown attenuation coefficient inside the body.

The talk by J. Schotland (joint with G. Bal) contained the development of a mathematical model for the case when incoherent light and standing ultrasound waves are used in AOT. An iterative algorithm is described for the cases of recovery the attenuation, or both the attenuation and the diffusion coefficient. It is expected that the reconstruction is well posed (stable), although numerical implementation and rigorous results are still to be developed.

W. Bangerth, who presented in his talk "Reconstructions in ultrasound modulated optical tomography" the joint work with M. Allmaras and P. Kuchment [2], addressed the case when coherence of the light is assumed (as it is in current experimental approaches) and the response at the ultrasound frequency of a boundary correlation function is used as the data. A mathematical model (which triggered an active discussion and some objections) was described and shown to work stably in numerical experiments, reconstructing rather sharp images, impossible in the regular OT. Although main uniqueness and stability questions are still open, a stability result for the linearized problem was described.

Another block of two lectures was devoted to the actively being developed Electron Microscope Tomography (ET) [13, 40, 41] in talks by A. Lawrence and by E. T. Quinto with co-authors.

A. Lawrence's talk "Advances in Large Field and High Resolution Electron Tomography", reflecting on the work done by his group at the Center for Research in Biological Systems of University of California, San Diego, provided an overview of the field and its challenges. The ET is used for constructing 3D views of sectioned biological samples, which are rotated around an axis and images are acquired for each "tilt" angle. It enables high resolution views of cellular and neuronal structures. ET 3D reconstruction encounters numerous challenges, including a low signal-to-noise ratio, curvilinear electron path, sample deformation (warping), scattering, magnetic lens aberrations, etc.

The talk "Electron Microscope Tomography" by E. T. Quinto (reflecting the results of his joint work with O. Öktem, U. Skoglund, and H. Rullgard) discussed ET from a mathematical perspective. Algorithms being developed and the microlocal analysis behind them were described. For small field ET, one can assume that the electrons travel over lines, and reconstructions that use this model were shown. However, for larger field ET, the electrons travel over curvilinear paths. A new mathematical model for this case was presented that involves a Radon transform over curvilinear paths. Microlocal analysis of this transform and reconstructions from real data, as well as theoretical underpinning of algorithms were presented.

Several lectures were devoted to other tomographic techniques or challenges.

S. Carney presented the talk "Deconstructing the Born series." A new method is proposed for directly obtaining from experiment the separate orders of the scattered fields from the exact scattered field. The approach applies to any system for which a solution may be cast as a Liouville-Neumann series. The method was simulated and shown to reduce multiple-scatter artifacts in linearized inverse scattering. It has potential to also be useful in so-called super-resolution problems.

The lecture "Problems in the diagnosis and treatment of breast cancer" was delivered by D. Isaacson. He discussed, in particular, how the ordering of the administration of drugs used in the chemotherapy of breast cancer can make a significant difference in the outcome.

A. Katsevich gave the lecture "An accurate approximate algorithm for motion compensation in two-dimensional tomography," in which he proposed an approximate inversion formula for motion compensation in tomography. The formula can be easily implemented numerically. Results of numerical experiments in the fan-beam case demonstrate good image quality even when motion is relatively strong.

V. Markel in his lecture "Inverse radiative transport with the method of rotated reference frames" presented the recently developed method of rotated reference frames. It allows one to obtain the plane-wave decomposition of the Green's function for the radiative transport equation in the slab geometry, which can be efficiently used to solve the linearized inverse problem for the RTE. Mathematical formulation of the method and its application to inverse problems and imaging were discussed and examples of image reconstruction with simulated and experimental data were presented.

S. Moskow delivered the lecture "The Inverse Born Series for Diffuse Waves" (joint work with J. Schotland). The inverse scattering problem for diffuse waves was considered. The results on convergence, stability and approximation error of the solution derived from inversion of the Born series, as well numerical simulations, were presented. The method has potential for being useful for other problems such as propagating scalar waves and Electrical Impedance Tomography.

In his lecture "Possibilities and limitations of ultrasound tomography," F. Natterer discussed the results of his recent work on ultrasound transmission and reflection imaging (e.g., [37, 38]). Mathematical issues, algorithms, and results of reconstructions were presented. It was concluded that the ultrasound tomography is currently close to clinical use, with reconstruction algorithms available for resolution down to 2mm. Reflection imaging was noted as a possible future development.

V. Palamodov's talk "Reconstruction in Doppler tomography" addressed the problem of recovering a vector field from some integral measurements. Such data arise in tomographic imaging of liquid or gas flows, tumor detection, optics and plasma physics, and other areas. The longitudinal line integrals of a vector field (or a 1-differential form f) form provide what is called Doppler transform. The reconstruction problem in Doppler tomography has some peculiarities, due to the object of reconstruction being more complex than a function. It was mentioned that the transform is gauge-invariant, i.e. all line integrals vanish for any exact form (irrotational part of the field). Thus, only reconstruction of the differential df is possible. The solenoidal part of f can be uniquely reconstructed from df. In $2D$, the problem reduces to Radon transform inversion, while in $3D$ the complete data is redundant. In the talk, some known results were discussed and it was shown that df can be recovered using acquisition geometry similar to the one used for recovering scalar functions. The method is extended to differential forms of arbitrary degree.

The talk "Micro-Tomographic Imaging of Coherent X-ray Scatter using a Polycapillary X-Ray Optic Imaging System and Multi-Energy X-Ray Detection" was delivered by E. Ritman. It was noticed that coherent scatter of X-rays can convey information about the chemical bonds in the material being irradiated, when the length of chemical bonds is of the order of an X-ray wave length. Consequently, the scatter can be used to discriminate certain chemical compounds (with similar atomic content) that have very similar X-ray attenuation coefficients. The scatter intensity can either be recorded as a function of angle (θ) from an illuminating, monochromatic, x-ray beam, or can be recorded by an energy-binning detector at one angle to a bremsstrahlung x-ray beam. Both methods provide a scatter intensity profile that is characteristic for the illuminated material, but its intensity must be corrected for attenuation of the illuminating beam, as well as of the scattered beam. Thus, a conventional CT image is needed to provide the attenuation map. Several modes of illumination and scatter recording that trade off signal-to-noise, speed of the data collection and need for Radon-type tomographic reconstruction from line integrals of the scatter were considered. If a collimator is used then line or sheet illumination can provide scatter data from known points within the 3D structure, so that no tomographic reconstruction is needed. If a non collimated detector array is used, or a volume is illuminated and scatter recorded via a collimator, then line integrals are recorded and the object has to be rotated in order to provide the data needed for Radon-type tomographic reconstruction. Polycapillary x-ray optics and energy selective imaging were used to generate tomographic image data that can discriminate polymeric materials with very similar attenuation coefficients.

4 Outcome of the Meeting

The meeting satisfied the need that existed for addressing the pressing issues of novel tomographic techniques. During the presentations and discussions, the current state of mathematical development of several emerging medical imaging modalities was surveyed and recent results and outstanding challenges were delineated.

The participants of the meeting were extremely actively involved into scientific discussions, especially during the evening panels, which have worked very efficiently. This has led to strengthening existing and forging new collaborations. There is no doubt that the meeting will facilitate the much needed progress in this practically important and mathematically challenging area.

Many presentation files are posted on the BIRS' Web site at
http://temple.birs.ca/˜09w5017/

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