Some Remarks on Applied Mathematics and the Imaging of the Brain

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November 2001

1 Introduction

Mathematics is one of the greatest intellectual creations of humanity. Indeed just like literature and art it transcends cultural barriers and has a universal value. It is a great intellectual achievement that also has elements of art. Most mathematicians will recognize "beauty" in mathematics.

There is a common misconception that in mathematics the essential discoveries have been made and all that remains is to apply the existing mathematical techniques to different domains. Nothing could be further from the truth. Actually the twentieth century witnessed enormous progress in mathematics. On the one hand physics, engineering, biology, medicine, finance, have all stimulated and continue to stimulate the discovery of new mathematics. On the other hand, mathematics generates its own internal problems (a great discovery is measured not only by the problems it solves but also by the new problems it creates). In the process of developing new powerful techniques, long-standing problems (such as the 300-year-old Fermat's Last Theorem) are solved and different areas of mathematics are unified.

In this note I will use brain imaging as an example of the usefullness of mathematics, and I will use the solution of certain PDEs as an example of a mathematical unification.

Until the advent of x-ray computerized tomography (CT), imaging studies provided only indirect visualization of the brain. The techniques that preceded CT include skull radiography and cerebral arteriography, which allowed examination of only the skull and the cerebral blood vessels, respectively. CT provided images of brain tissue directly, and the subsequent development of magnetic resonance imaging (MRI) allowed striking discrimination between gray and white matter. The mathematics of the CT will be reviewed in §2.

The above techniques were capable of imaging only the structure of the brain. The development of the functional MRI and of the positron emission tomography (PET) in the later 80's allowed researchers to begin to study the functional characteristics of the brain. Until this remarkable development, neurophysiologists gathered data by poking electrodes into the brains of experimental animals and into the human brains during neurosurgery, while psychologists and psychiatrists studying the "human mind", treated the brain largely as a black box. Now it is possible to observe noninvensively neural activity in living humans with ever-increasing precision. For the first time it is possible to delineate which particular brain areas are associated with a particular higher cortical activity. For example, it has been shown that women use both sides of their brain in processing language while men rely chiefly on the left brain; musicians have an unusual asymmetry in the auditory cortex, etc. Both fMRI and PET have an excellent spatial resolution (of the order of millimeters) but poor time resolution (of the order of seconds). Magnetoencephalography (MEG) is another functional imagining technique, which has excellent time resolution but at the moment poor spatial resolution. The mathematics of MEG will be reviewed in §3.

Perhaps the most important application of mathematics is the solution of mathematical equations. Among such equations, partial differential equations play a prominent role. A new transform method for solving a large class of PDEs will be briefly mentioned in §4. As an example of unification, we note that the mathematical formalisms mentioned here, namely the mathematics of CT, of MEG, and of the transforms for solving PDEs, are deeply related.

2 Brain Anatomy

The discovery of x-rays had an important impact on several areas of clinical medicine. However, since the brain is enclosed by the skull, x-rays were ineffective for the imaging of the brain. In the late seventies, the advent of computerized tomography (CT) led to the first direct visualization of brain tissue. CT and magnetic resonance imaging (MRI), which was developed later, have had a tremendous impact on neurology and psychiatry.

Computerized tomography is the computer-aided reconstruction of a function from its line integrals. The most prominent application of CT is still diagnostic radiology. Here, a cross-section of the human body is scanned by a thin x-ray beam whose intensity loss is recorded by a detector and processed by a computer to produce a two-dimensional image which in turn is displayed on a screen.

A simple physical model is based on Beer's law: Let $f(x,y)$ be the x-ray attenuation coefficient of the tissue at the point (x,y), i.e. x-rays transversing a small distance Δs at (x,y) suffer a relative intensity loss

$$\frac{\Delta I}{I} = -f\Delta s.$$

In the limit this becomes the first order ordinary differential equation

$$\frac{dI}{ds} = -f(x(s),y(s))I.$$

Thus

$$I = ce^{-\int f ds}, \quad c \text{ constant.} \tag{2.1}$$

Let I_0 be the initial intensity of the beam L, which we think of as a straight line, and let I_1 be its intensity after having passed the body. Equation (2.1) implies

$$I_1 = I_0 e^{-\int_L f ds},$$

or

$$\ln\left(\frac{I_0}{I_1}\right) = \int_L f(x(s),y(s))ds. \tag{2.2}$$

The mathematical problem in CT is the following: Given I_0/I_1 for all lines, reconstruct $f(x,y)$.

The line integral of a function is called its Radon transform. Radon in 1917 gave an explicit inversion formula, although it appears that both the Radon transform and its inversion formula were known to Lorenz around 1900. A line can be specified by its "distance" l from the origin and by a unit vector $\mathbf{k}$. If $\tan^{-1} k$ is the angle of the line L with the x-axis, then a point (x,y) on this line is given by

$$\left(\frac{s-lk}{\sqrt{1+k^2}}, \frac{sk+l}{\sqrt{1+k^2}}\right),$$

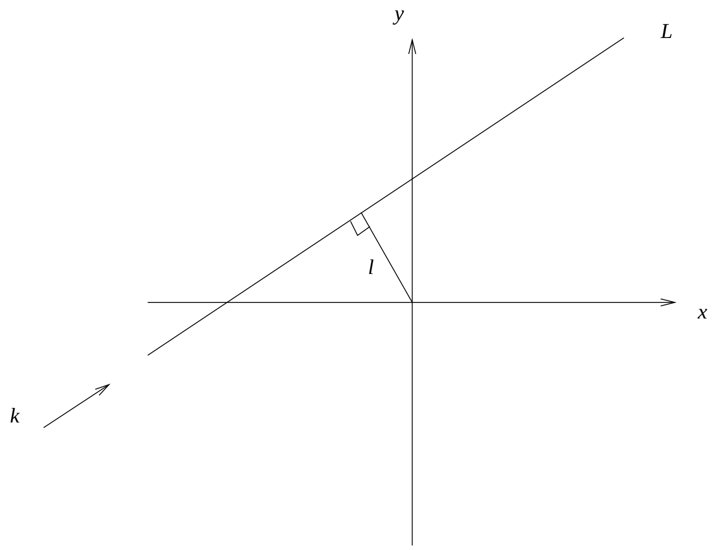

Figure 1:

where s is a parameter on this line. Thus the rhs of equation (2.2) becomes

$$\int_{-\infty}^{\infty} f\left(\frac{s-lk}{\sqrt{1+k^2}}, \frac{sk+l}{\sqrt{1+k^2}}\right) ds. \tag{2.3}$$

Denoting this integral by $\tilde{f}(k,l)$, we can formulate the inversion problem as follows: Given the integral (2.3) for all lines, i.e. given $\tilde{f}(k,l)$ for all (k,l), find f. The explicit solution of this "inverse problem" is given by

$$f(x,y) = \frac{1}{2\pi^2}\frac{\partial}{\partial y}\int_{-\infty}^{\infty} dk \fint_{-\infty}^{\infty} \frac{\tilde{f}(k,l)}{y-kx-l\sqrt{1+k^2}}\, dl. \tag{2.4}$$

We note that the Radon transform is closely related with the two-dimensional Fourier transform,

$$\hat{f}(k,l) = \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dy e^{-ikx-ily} f(x,y)\, dx\, dy; \tag{2.5a}$$

we recall that the inversion formula for this transform is

$$f(x,y) = \frac{1}{(2\pi)^2}\int_{-\infty}^{\infty} dk \int_{-\infty}^{\infty} dl e^{ikx+ily}\hat{f}(k,l). \tag{2.5b}$$

Actually one way of deriving equation (2.4) is to exploit this relation between the Radon and the Fourier transform.

In practice the relevant integrals can be measured only for a finite number of lines L. Thus the real problem in CT is to reconstruct f from a finite number of its line integrals. This problem depends on the particular way that this finite number of lines is chosen. This is determined by the design of the scanner and is referred to as scanning geometry. The first such geometry used was parallel scanning, i.e. a set of equally spaced parallel lines are taken for a number of equally

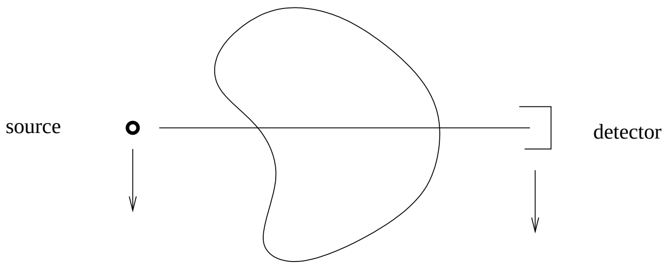

Figure 2:

distributed directions. It requires a single source and a single detector which move in parallel and rotate during scanning. Parallel scanning was used by A. Cormack in 1963 and the first commercial scanner was developed by G. Hounsfield. Today this form of scanning has been replaced by fan-beam scanning: The source runs on a circle around the body, firing a fan of x-rays which are recorded by a linear detector array simultaneously for each source position.

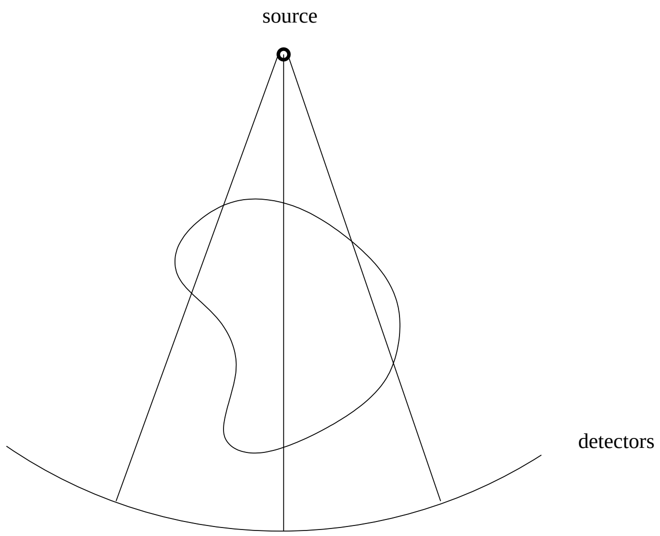

Figure 3:

The main mathematical problems associated with the "finite scanning" are: (a) the impact of finite sampling and of the scanning geometry on resolution and accuracy; (b) uniqueness and stability of the reconstruction methods for incomplete data [1].

3 Brain Dynamics

Positron Emission Tomography and Functional Magnetic Resonance

The first step in positron emission tomography (PET) scans, is to inject the patient with a dose of a radiopharmaceutical. For example, flurodeoxyglucose (FDG) is a normal molecule of glucose attached artificially to an atom of radioactive fluorine. The cells in the brain which are more active have a higher metabolism, need more energy, thus will absorb more FDG. The fluorine atom in the FDG molecule suffers a radioactive decay, emitting a positron. When a positron collides with an electron it liberates energy in the form of two beams of gamma rays (in opposite direction) which are picked by the PET scanner.

fMRI is based on the responses of protons in a strong magnetic field to the effect of a brief radiofrequency pulse. Within the magnetic field, protons of the body align the axis of their nuclear spins with the external magnetic field and are displaced from this alignment by the radiofrequency pulse. When the pulse ends, the protons return to their previous orientation in the magnetic field, and radiofrequency energy is emitted from the tissue. The energy is amplified, recorded, and transformed into a planar or three-dimensional image of the structures studied. The nuclear magnetic resonance signal is influenced by the oxygenation of the blood: deoxygenation of the blood produces deoxyhaemoglobin, which contains a different form of iron than haemoglobin; this leads to a change in the intensity of the nuclear magnetic resonance signal [2].

The mathematical tool used in the inversion problem of the fMRI is the two-dimensional Fourier transform and its discrete version the Fast Fourier transform.

From the above discussion it follows that the positron emission scan is "glucose consumption dependent", while the functional magnetic resonance imaging is "blood-oxygen-level-dependent". However, the precise relationship between the PET scan and the fMRI responses and the underlying neural activity is unclear. Progress in this direction was made this year by the group of N. Logothetis [3] at the Max Planck Institute using simultaneously fMRI and electrical recording techniques in the visual cortex of monkeys. Using sophisticated electrical recording techniques this group was able to distinguish between several aspects of neuronal activity and in particular between the action potentials and the local field potentials. The former are the all-or-nothing firing rates of individual neurons and groups of neurons; they occur immediately after a stimulus has been presented and reflect neuronal output. Local field potentials are the more slowly varying electrical potentials that arise from the input, and integrative processes within neurons. The major determinant of the fMRI signal turned out to be the local field potentials. The new question then becomes: What is the mechanism which leads to increased blood flow and increased glucose consumption, but also to increased oxygen level? At rest the human brain uses up to 20% of the oxygen needed by the body (although it accounts for less than 2% of the body's mass); this oxygen is used to break down glucose to supply the brain with energy. But for the brief increase in the activity of particular brain regions, the glucose is broken down *anaerobically*, by the *rapid* process of glycolysis. Thus increased activity leads to increases in blood flow and glucose consumption which far exceed the increase in oxygen consumption. Thus, since supply exceeds demand, there exists a local increase in the available amount of oxygen. Recent work has also offered a tentative explanation for the local increase in glycolysis: The communication between neurons occurs at synapses and requires the release of neurotransmitters from a presynaptic neuron to the postsynaptic nerve cell. The amino acid glutamate is the main excitatory neurotransmitter in the brain. After it is released in the synaptic cleft, it is removed through its uptake by an adjacent non-neuronal cell called astrocyte. There glutamate must be converted to glutamine before it can be transported to the neuron and recycled. The energy needed for processing glutamate is provided by glycolysis. In summary, local activation of an area of the brain yields increases in the processing of glutamate, which needs rapid glucose consumption provided by glycolysis, which since is anerobic yields to an increase of the available oxygen.

Magnetoencephalography

Magnetoencephalography (MEG) measures the magnetic field generated by the neuronal electrical activity in the brain, and attempts to reconstruct the electric current from this measurement. The main difficulty in measuring the magnetic field is that it is extremely weak, of the order of femto Tesla, and is of the order of 10^{-9} of the earths geomagnetic field. This difficulty is bypassed by using the Superconducting Quantum Interference Device (SQUID). This is the most sensitive detector of any kind available to scientists. It was constructed in the late 1960's by J. Zimmerman, and it was first used for the measurement of the magnetic field of the brain in the late 1970's by D. Cohen. The SQUID is based on the exploitation of several quantum-mechanical effects, among which the most important are superconductivity and the Josephson effect. The SQUID can be thought of as a digital magnetometer where each "digit" represents one flux quantum. It is essentially a transducer converting a tiny change in magnetic flux into voltage. Until the middle 1980's all biomagnetic measurements were carried out using single-channel magnetometers (i.e. the magnetic flux was measured only at one point). However, in the new generation of SQUIDs it is possible to make measurements simultaneously at about 200 points.

A simple physical model is based on Maxwell's equations:

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0}, \quad \nabla \wedge \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \tag{3.1}$$

$$\nabla \cdot \mathbf{B} = 0, \quad \nabla \wedge \mathbf{B} = \mu_0 \left(\hat{\mathbf{J}} + \varepsilon_0 \frac{\partial \mathbf{E}}{\partial t} \right), \tag{3.2}$$

where $\mathbf{E}$ is the electric field, $\mathbf{B}$ the magnetic field, $\hat{\mathbf{J}}$ the total current density, ρ the charge density and ε_0, μ_0 are the permittivity and permeability of free space respectively. Also

$$\hat{\mathbf{J}} = \mathbf{J} + \sigma \mathbf{E}, \quad \mathbf{P} = (\varepsilon - \varepsilon_0)\mathbf{E}, \tag{3.3}$$

where $\mathbf{J}$ is the neuronal current, $\mathbf{P}$ is polarization, σ is the conductivity and ε is the permitivity of the medium.

Let $\mathbf{E} = \mathbf{E}_0(\mathbf{x}) \exp[2\pi i f t]$. In the brain

$$\sigma \sim 0 \cdot 3\Omega^{-1} m^{-1}, \quad \varepsilon \sim 10^5 \varepsilon_0, \quad f \sim 100 \text{ Hz},$$

thus $\frac{\partial \mathbf{E}}{\partial t}$ can be neglected (quasistatic approximation); similarly $\frac{\partial \mathbf{B}}{\partial t}$ can also be neglected. This yields

$$\nabla \wedge \mathbf{B} = \mu_0 \mathbf{J}, \quad \nabla \wedge \mathbf{E} = 0. \tag{3.4}$$

The second equation implies

$$\mathbf{E} = -\nabla V, \tag{3.5}$$

where the scalar function V is called the voltage potential.

Assuming further that $\sigma = \sigma_1$ inside the head, $\sigma = \sigma_0$ outside the head, where σ_1, σ_0, are constants, and that the permeability of the head equals μ_0 which is constant, equations (3.2a), (3.3a), (3.4a), (3.5), yield the Geselowitz equation [4],

$$\mathbf{B}(\mathbf{x}) = \frac{\mu_0}{4\pi} \int_\Omega \mathbf{J}(\mathbf{y}) \wedge \frac{\mathbf{x} - \mathbf{y}}{|\mathbf{x} - \mathbf{y}|^3} d\mathbf{y} - \frac{\mu_0}{2\pi} (\sigma_I - \sigma_0) \int_{\partial\Omega} V(\mathbf{y}) \mathbf{n}(\mathbf{y}) \wedge \frac{\mathbf{x} - \mathbf{y}}{|\mathbf{x} - \mathbf{y}|^3} dS, \tag{3.6}$$

where $\mathbf{x}$ is outside Ω, Ω denotes the volume occupied by the head, $\partial\Omega$ denotes the boundary of Ω, and $\mathbf{n}(\mathbf{y})$ is the outward unit normal to $\partial\Omega$.

If one makes the further approximations that the head is spherical, and that $\sigma_0 = 0$ (which is consistent with $\sigma_0 << \sigma_I$), it can be shown [5] that equation (3.6) reduces to

$$\mathbf{B} = \mu_0 \nabla U, \tag{3.7a}$$

$$U(\mathbf{x}) = \frac{1}{4\pi} \int_{|\mathbf{y}|\le 1} \frac{\mathbf{J}(\mathbf{y}) \wedge \mathbf{y} d\mathbf{y}}{|\mathbf{x}-\mathbf{y}|(|\mathbf{x}||\mathbf{x}-\mathbf{y}| + \mathbf{x}\cdot(\mathbf{x}-\mathbf{y}))} \cdot \mathbf{x}, \quad |\mathbf{x}| > 1. \tag{3.7b}$$

The mathematical problem in MEG is: Given U, determine $\mathbf{J}$. However it is well known that the problem of determining $\mathbf{J}(\mathbf{y})$, $|\mathbf{y}| \le 1$, from the knowledge of $U(\mathbf{x})$, $|\mathbf{x}| > 1$, is nonunique. For example, it is obvious from equation (3.7b) that the radial part of the current does not affect $U(\mathbf{x})$. A complete answer of the nonuniqueness question was given in [6]:

The current $\mathbf{J}$ *can be uniquely represented in the form*

$$\mathbf{J} = J^\rho \mathbf{e}_\rho + \frac{1}{\rho}\left(\frac{\partial G}{\partial \theta} - \frac{1}{\sin\theta}\frac{\partial F}{\partial \varphi}\right)\mathbf{e}_\theta + \frac{1}{\rho}\left(\frac{1}{\sin\theta}\frac{\partial G}{\partial \varphi} + \frac{\partial F}{\partial \theta}\right)\mathbf{e}_\varphi, \tag{3.8}$$

where $\mathbf{e}_\rho$, $\mathbf{e}_\theta$, $\mathbf{e}_\varphi$ *are the unit vectors associated with the spherical coordinates* (ρ, θ, φ), *and* J^ρ, G, F *are scalar functions of* (ρ, θ, φ). *Using this representation, equation (3.7b) becomes*

$$U(\mathbf{x}) = \int_{|\mathbf{y}|\le 1} \frac{1}{|\mathbf{x}-\mathbf{y}|}\left(\frac{1}{|\mathbf{y}|^2}\int_{|\mathbf{y}|}^{1} (\Delta_{\theta,\varphi}F)(\rho,\theta,\varphi) d\rho\right) d\mathbf{y}, \tag{3.9}$$

where (ρ, θ, φ) *are the spherical coordinates of* $\mathbf{y}$, *and* $\Delta_{\theta,\varphi}$ *denotes the Laplacian with respect to the spherical coordinates.*

Equation (3.9) implies that knowledge of $U(\mathbf{x})$ yields only certain moments of F. The first impression of this result is that perhaps magnetoencephalography is of limited use. However, it was also shown in [6] that if one assumes that $\mathbf{J}$ is such that energy is minimized, then $\mathbf{J}$ is indeed unique:

Given $U(\mathbf{x})$, *there exists a unique solution* $\mathbf{J}$ *which satisfies equation (3.7b) and which minimizes the energy functional*

$$W(\mathbf{J}) = \int_{|\mathbf{y}|\le 1} |\mathbf{J}|^2 d\mathbf{y}.$$

This unique solution is given by

$$J = -\frac{1}{\rho \sin\theta}\frac{\partial F}{\partial \varphi}\mathbf{e}_\theta + \frac{1}{\rho}\frac{\partial F}{\partial \varphi}\mathbf{e}_\varphi,$$

where the function F *is given by*

$$F = \sum_{l,m} \frac{(2l+1)(2l+3)}{l} C_{l,m} \rho^{l+1} Y_{l,m}(\theta, \varphi),$$

$Y_{l,m}$ *are the usual spherical harmonics, and the constants* $C_{l,m}$ *are determined from the measurement via*

$$U = \sum_{l,m} C_{l,m} \rho^{-(l+1)} Y_{l,m}(\theta, \varphi).$$

4 Transform Methods for PDE's

It was mentioned in §2 that the Radon transform is intimately related to the two-dimensional Fourier transform (FT). An important application of transforms is the solution of PDE's. For example, the initial value problem of the equation

$$iq_t + q_{xx} = 0, \quad -\infty < x < \infty, \quad t > 0, \tag{4.1}$$

$$q(x,0) = q_0(x),$$

where $q_0(x)$ decays as $|x| \to \infty$, can be solved by the one-dimensional FT. This transform is intimately related with the equation

$$\mu_x - ik\mu = q(x), \quad -\infty < x < \infty. \tag{4.2}$$

Indeed, there exists an algorithmic way of obtaining the one-dimensional FT and its inverse by performing the spectral analysis of equation (4.2) [7].

It is remarkable that there exists a "nonlinearization" of transforms. For example a "non-Abelian" form of equation (4.2) is

$$\mu_x - ik \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix} \mu = \begin{pmatrix} 0 & q \\ \bar{q} & 0 \end{pmatrix} \mu, \quad -\infty < x < \infty, \tag{4.3}$$

where μ is now a 2×2 matrix and bar denotes complex conjugation. In analogy with equation (4.2) there exists an alogorithmic way of obtaining from equation (4.3) a "nonlinear FT" and its inverse. This nonlinear transform can be used to solve the Cauchy problem for the nonlinear Schrödinger equation

$$iq_t + q_{xx} - 2|q|^2 q = 0, \quad -\infty < x < \infty, \quad t > 0,$$

$$q(x,0) = q_0(x). \tag{4.4}$$

Similar considerations are valid in multidimensions. For example the two-dimensional FT can be obtained by analysing the equation

$$\mu_x + i\mu_y - k\mu = q, \quad -\infty < x < \infty, \quad -\infty < y < \infty. \tag{4.5}$$

In the same way that the two-dimensional FT can be used to solve two-spatial dimensional extensions of equation (4.1), the "non-Abelian" analogue of equation (4.5) can be used to derive a "nonlinear two dimensional FT", which can be used to solve certain nonlinear PDE's in two spatial dimensions [8].

The Radon transform can be obtained by analysing the equation

$$\mu_x - k\mu_y = q(x,y), \quad -\infty < x < \infty, \quad -\infty < y < \infty. \tag{4.6}$$

It can be used for the solution of certain problems associated with Maxwell's equations. It is remarkable that there exists a "nonlinear Radon transform", derived from the spectral analysis of the "non-Abelian" analogue of equation (4.6), namely

$$\mu_x - k\mu_y = q(x,y)\mu,$$

(μ is an $N \times N$ matrix), which can be used for the solution of the celebrated Yang-Mills equations.

Transform solutions of PDEs are based on the fundamental idea of separation of variables, which essentially reduces the analysis of a PDE in two dimensions to the analysis of two ODE's. This in turn is based on the general philosophical principle of reducing a complicated problem to a simpler one. This idea has been recently challenged by the author, who has presented a new transform method which *does* not reduce the PDE to two ODEs. In its simplest form this new method is based on the realization that, for example, equation (4.1) is equivalent to the pair

$$\mu_x - ik\mu = q$$

$$\mu_t + ik^2\mu = iq_x - kq. \tag{4.7}$$

It was already mentioned that the analysis of equation (4.7a) yields an x-transform. Similarly the analysis of equation (4.7b) yields a t-transform. The new method involves analysing both equations (4.7) *simultaneously.* This gives rise to a *new transform*; this transform can be used *only* for the solution of equation (4.1). However, precisely because it is "custom made" it has important advantages over both the x- and t-transforms. The nonlinearization of this new type of transform is discussed in [8].

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