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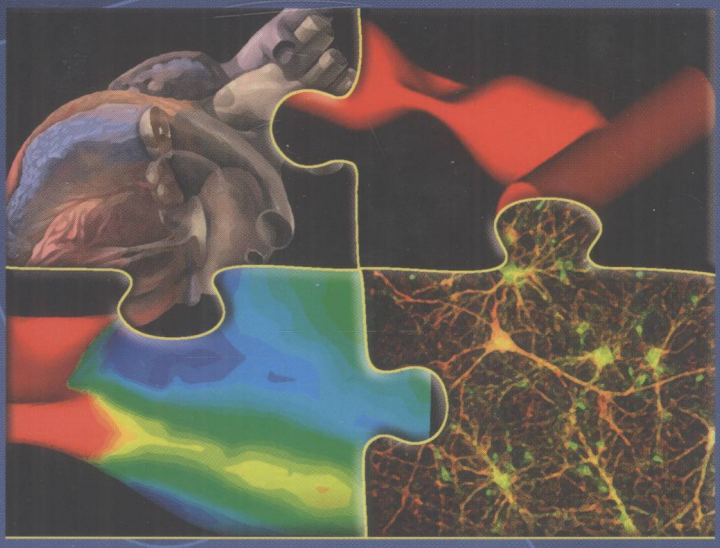
Complex Systems in Biomedicine



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Complex Systems in Biomedicine

With 88 Figures

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The picture on the cover shows an integration of a synapsis (bottom right), the computational domain for a pulmonary artery bifurcation (top right), the human heart (top left), and the wall shear stress in a pulmonary artery (bottom left).

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Preface

Mathematical modeling of human physiopathology is a tremendously ambitious task. It encompasses the modeling of most diverse compartments such as the cardiovascular, respiratory, skeletal and nervous systems, as well as the mechanical and biochemical interaction between blood flow and arterial walls, and electrocardiac processes and electric conduction in biological tissues. Mathematical models can be set up to simulate both vasculogenesis (the aggregation and organization of endothelial cells dispersed in a given environment) and angiogenesis (the formation of new vessels sprouting from an existing vessel) that are relevant to the formation of vascular networks, and in particular to the description of tumor growth.

The integration of models aimed at simulating the cooperation and interrelation of different systems is an even more difficult task. It calls for the setting up of, for instance, interaction models for the integrated cardio-vascular system and the interplay between the central circulation and peripheral compartments, models for the mid-to-long range cardiovascular adjustments to pathological conditions (e.g., to account for surgical interventions, congenital malformations, or tumor growth), models for integration among circulation, tissue perfusion, biochemical and thermal regulation, models for parameter identification and sensitivity analysis to parameter changes or data uncertainty – and many others.

The heart is a complex system in itself, where electrical phenomena are functionally related to wall deformation. In its turn, electrical activity is related to heart physiology. It involves nonlinear reaction-diffusion processes and provides the activation stimulus to heart dynamics and eventually the blood ventricular flow that drives the haemodynamics of the whole circulatory system. In fact, the influence is reciprocal, since the circulatory system in turn affects heart dynamics and may induce an overload depending upon the individual physiopathologies (for instance, the presence of a stenotic artery or a vascular prosthesis).

Virtually all the fields of mathematics have a role to play in this context. Geometry and approximation theory provide the tools for handling clinical data acquired by tomography or magnetic resonance, identifying meaningful geometrical patterns and producing three-dimensional geometric models stemming from the original patient's data. Mathematical analysis, fluid and solid dynamics, stochastic analysis are used to set up the differential models and predict uncertainty. Numerical analysis and high performance computing are needed to solve the complex differential models numerically. Finally, methods from stochastic and statistical analysis are exploited for the modeling and interpretation of space-time patterns.

Indeed, the complexity of the problems at hand often stimulates the use of innovative mathematical techniques that are able, for instance, to capture accurately those processes that occur at multiple scales in time and space (such as cellular and systemic effects), and that are governed by heterogeneous physical laws.

In this book we have collected the contributions of several Italian research groups that are successfully working in this fascinating and challenging field. Each chapter deals with a specific subfield, with the aim of providing an overview of the subject and an account of the most recent research results.

Chapter 1 addresses a class of inverse mathematical problems in biomedical imaging. Imaging techniques (such as tomography or magnetic resonance) are a powerful tool for the analysis of human organs and biological systems. They invariably require a mathematical model for the acquisition process and numerical methods for the solution of the corresponding inverse problems which relate the observation to the unknown object.

Chapter 2 addresses those biochemical processes which are composed of two phases, generation (nucleation, branching, etc.) and subsequent growth of spatial structures (cells, vessel networks, etc), which display , in general, a stochastic nature both in time and space. These structures induce a random tessellation as in tumor growth and tumor-induced angiogenesis. Predictive mathematical models which are capable of producing quantitative morphological features of developing tumor and blood vessels demand a quantitative description of the spatial structure of the tessellation that is given in terms of the mean densities of interfaces.

A preliminary stochastic geometric model is proposed to relate the geometric probability distribution to the kinetic parameters of birth and growth. For its numerical assessment, methods of statistical analysis are proposed for the estimation of the geometric densities that characterize the morphology of a real system.

Chapter 3 presents a review of models of tumor growth and tumor treatment. One family of models concerns blood vessels collapsing in vascular tumors, another is devoted to the modeling of tumor cords (growing directly around a blood vessel), highlighting features that are relevant in the evolution of solid tumors in the presence of necrotic regions. Tumor cords are also taken as an example of how to deal with certain aspects of tumor treatment.

The aim of Chapter 4 is the description of models that were recently developed to simulate the formation of vascular networks which occurs mainly through the two different processes of vasculogenesis and angiogenesis. The results obtained by mathematical models are compared with in vitro and in vivo experimental results. The chapter also describes the effects of the environment on network formation and investigates the possibility of governing the network structure through the use of suitably placed chemoattractants and chemorepellents.

Chapter 5 deals with mathematical models of cardiac bioelectric activity at both cellular and tissue levels, their integration and their numerical simulation. The so-called macroscopic bidomain model of the myocardium tissue is derived by a two-scale homogenization method, and is coupled with extracardiac medium and extracardiac potential. These models provide a base for the numerical simulation of anisotropic cardiac excitation and repolarization processes.

In Chapter 6 the authors discuss the role of delay differential equations for describing the time evolution of biological systems whose rate of change depends on their configuration at previous time instances. A noticeable example is the Waltman model which describes the mechanisms by which antibodies are produced by the immune system in response to an antigen challenge.

In the last Chapter the authors illustrate recent advances on the modeling of the human circulatory system. More specifically, they present six examples for which numerical simulation can help to provide a better understanding of physiopathologies and a better design of medical tools such as vascular prostheses and even to suggest possible alternative procedures for surgical implants. Each example provides the conceptual framework for introducing mathematical models and numerical methods whose applicability, however, goes beyond the specific case addressed.

This chapter aims as well to provide an account of successful interdisciplinary research between mathematicians, bioengineers and medical doctors.

We are well aware that this is simply a preliminary contribution to a mathematical research field which is growing impetuously and will attract increasing attention from medical researchers in the years to come.

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February 2006

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Contents

Inverse problems in biomedical imaging: modeling and methods of solution

M. Bertero, M. Piana

Abstract. Imaging techniques are a powerful tool for the analysis of human organs and biological systems and they range from different kinds of tomography to different kinds of microscopy. Their common feature is that they require mathematical modeling of the acquisition process and numerical methods for the solution of the equations relating the data to the unknown object. These problems are usually named inverse problems and their main feature is that they are ill-posed in the sense of Hadamard, so that their solutions require special care. In this chapter we sketch the main issues which must be considered when treating inverse problems of interest in biomedical imaging.

Keywords: inverse problems, tomography, image deconvolution, regularization and statistical methods, iterative reconstruction methods.

1 Introduction

The invention of Computed Tomography (CT) by G. H. Hounsfield at the beginning of the seventies was a breakthrough in medical imaging comparable to the discovery of X-rays by W. C. Roengten in 1895. Even if CT and radiography derive from the same physical phenomenon, the conception of CT was based on ideas which opened new and wide perspectives. Indeed, CT requires mathematical modeling of X-ray absorption, in order to provide equations which relate the observed data to the unknown physical parameters, and methods for the solution of these equations. In such a way it is possible to exploit the tremendous amount of information contained in radiographic data: a 3D image of the human body can be obtained, descerning variations in soft tissue such as the liver and pancreas, and measuring in a quantitative way the density variations of the different tissues. An accuracy of few percent can be obtained with a resolution of the order of 1 mm.

The new ideas introduced in CT were soon transferred to other methods for imaging human tissues. The first was Magnetic Resonance (MR), which is based on the detection of the signals emitted by the magnetic moments of hydrogen nuclei when polarized by means of suitable static magnetic fields and excited by radiofrequency signals under resonance conditions. Moreover, earlier scintigraphic methods evolved into the functional imaging techniques known as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). In these cases a radio-pharmaceutical is administered to the patient and its distribution, due to metabolic processes, is investigated by detecting the γ-rays emitted by the radionuclides. As we briefly discuss at the end of this chapter, the development of other techniques, based, e.g., on microwaves and on infrared radiation, is in progress.

In general, the new techniques of medical imaging are based on the interrogation of the human body by means of radiation transmitted, reflected or emitted by the body: the effect of the body on the radiation is observed, a mathematical model for the body-radiation interaction is developed and the equations provided by this model are solved in post-processing of the observed data. The same approach applies to cell imaging by means of fluorescence or electron microscopy.

We emphasize a specific requirement of medical imaging, namely, the need for a solution in almost real time. In general a refined model of body-radiation interaction leads to complex non-linear equations, whose solution may require hours of computation time on a powerful computer. Hence the need to develop sufficiently accurate linear models, whenever this is possible, or also to design the observation process in such a way that a linear approximation is feasible. For this reason linearity is the first issue we discuss in this chapter (Sect. 2).

A second specific feature of biomedical imaging is that the problems to be solved are ill-posed in the sense of Hadamard. As we discuss in Sect. 3, being ill-posed implies that it is meaningless to look for exact solutions and that, nevertheless, the set of approximate solutions is too broad to be significant. In other words, although the data at our disposal can contain a tremendous amount of information, the fact that the problem is ill-posed, combined with the presence of noise, implies that the extraction of this information is not trivial.

A very important consequence of being ill-posed is that mathematical modeling of the medical imaging process cannot uniquely consist in establishing the equations relating the data to the solution; it must also include a model of the noise perturbing the data and, as far as possible, a model of known properties of the solution. Indeed the modeling of the noise is needed in order to clarify in what sense one is looking for approximate solutions; on the other hand the modeling of the solution properties must be used for extracting meaningful solutions from the broad set of approximate ones. Therefore noise and "a priori" information on the solution are two other important issues to be considered in biomedical imaging. These are discussed in Sect. 4 and Sect. 5 respectively. In Sect. 6 we outline the main computational issues concerned with the solution procedure and the solution methods which are most frequently used in practice and, lastly, in Sect. 7 we provide a brief description of some of the current medical imaging techniques in progress.

Before concluding this introduction we briefly describe two important examples which can be used as reference cases for the general treatments described in subsequent sections: the first is X-ray tomography and the second fluorescence microscopy.

1.1 X-ray tomography

In the case of X-ray tomography we adopt a tutorial approach which does not correspond exactly to the data acquisition geometry in CT scanners. Therefore we assume that we have a source S emitting a well collimated X-ray beam; the beam crosses the body to be imaged and, at exit, its intensity is measured by a detector D. The attenuation of the X-rays across the body is described by the following simple model:

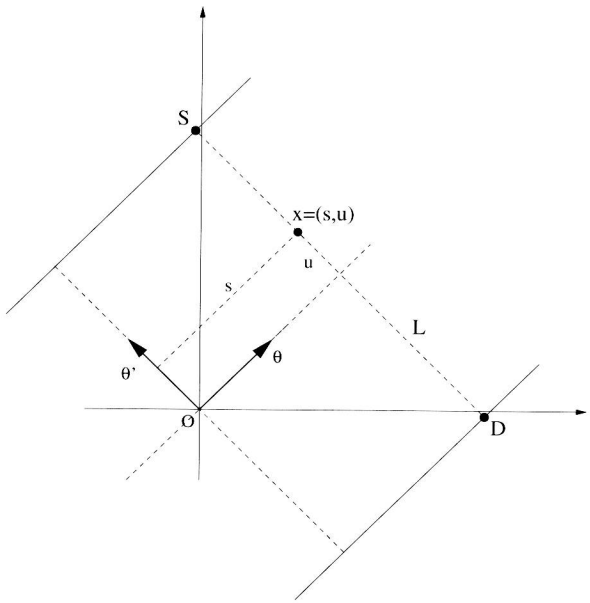

Fig. 1. Geometry of data acquisition in X-ray CT. The source S and the detector D move along two parallel straight lines with direction θ. The line L, joining S and D, is the integration line, with direction θ', orthogonal to θ. A point x of L has coordinates $\{s, u\}$ with respect to the system formed by θ, θ'

let $f(x)$ be the attenuation coefficient at point x (roughly proportional to the density of the tissue at x); then, if u is a coordinate along the straight line L joining S and D (see Fig. 1), the intensity loss at x is given by:

$$\frac{dI}{du}(x) = -f(x)I(x),$$

where I is the intensity measured by D.

It follows that, if I_0 is the intensity emitted by S, then

$$I = I_0 \exp\left\{-\int_L f(x)du\right\},$$

so that the logarithm of the ratio between the intensities of the emitted and detected radiation is just the line integral of the attenuation coefficient. By moving the S-D system along two parallel lines, the plane to be imaged is defined, and, by measuring the intensity for all the positions, one gets what is called a projection of the unknown function $f(x)$. More precisely, if θ is the unit vector in the direction of the movement of the S-D system (linear scanning), s the distance (with sign) of L from the origin of the coordinate system (see Fig. 1), and θ' the unit vector in the orthogonal direction, then the *projection of f in the direction θ* is given by

$$(P_\theta f)(s) = \int f(s\theta + u\theta')du. \tag{1}$$

By rotating the *S-D* system and repeating the linear scanning for all possible angles (angular scanning) one obtains all possible projections and the result is the (two-dimensional) *Radon transform* of the function f: $(Rf)(s,\theta) = (P_\theta f)(s)$. These are just the data of X-ray CT, obtained by combining the linear and angular scanning as described above. Then, in order to get the function f, one has to solve the linear equation

$$g(s,\theta) = (Rf)(s,\theta),$$

where $g(s,\theta)$ denotes the measured data. This problem was solved by Radon in 1917 [59] and its inversion formula in the 2D case can be written as follows [57]:

$$f(x) = \frac{1}{4\pi^2}\int_{S^1} P\int_{R^1} \frac{1}{x\cdot\theta - s}\frac{\partial g}{\partial s}(s,\theta)dsd\theta, \tag{2}$$

where P denotes the principal value. This formula clearly shows that the inversion of the Radon transform is an ill-posed problem since it requires the computation of the derivative of (noisy) data. Moreover the *filtered backprojection algorithm*, first introduced by Bracewell and Riddle [9] in radio astronomy and now widely used in medical imaging, is just a clever implementation of this formula.

The 3D imaging is obtained by repeating the previous procedure for different planes, namely, by scanning in the z-direction also, orthogonal to the imaging plane. Therefore the data of the problem depend on the variables $\{s,\theta,z\}$, which essentially characterize the position of the *S-D* system. These data can be called the *image* of f, as provided by the CT scanner. For a given z the representation of g in the plane $\{s,\theta\}$ is the so-called *sinogram*. We give an example in Fig. 2. It is obvious that the interpretation of these data without the help of a reconstruction algorithm is impossible. As text books in tomography we mention the books of Kak and Slaney [42] and Natterer [56].

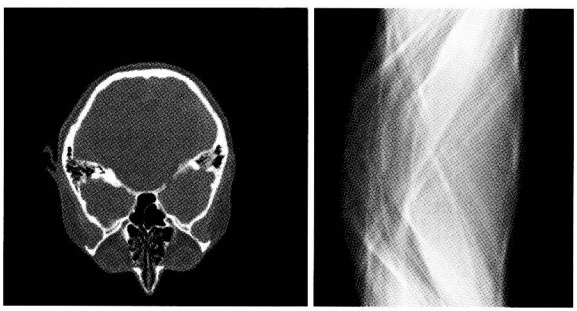

Fig. 2. Left-hand panel: tomographic reconstruction of a section of a human head. Right-hand panel: the corresponding sinogram