

Diagnostic system of coronary artery disease: parameter identification tasks and treatment of tracer kinetic problems by using integral equations

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We are developing a diagnostic computer system for patient-specific simulation studies of the flow of blood in the entire coronary circulation which comprises the epicardial arteries on the surface of the heart, the intramyocardial arteries, and the venous system. In coronary artery disease, only pathological changes of the arterial system play a decisive role. In the epicardial arteries, especially around sections with stenoses (narrowing), the blood flow is simulated three-dimensionally. In the other parts of the coronary circulation, however, we preferably use lumped parameter simulation models. The patient-specific simulation studies are based on information contained in medical images. In particular, the geometry of the epicardial arteries is derived from biplane angiograms, whereas the structure (geometry) and other specific properties of the intramyocardial vessels are deduced essentially from information contained in PET perfusion images.

The creation of a patient-specific simulation model of the intramyocardial part of the coronary circulation based on PET perfusion images is a quite difficult task, since it leads to solving awkward inverse problems. Mathematically it means that we have to solve systems of nonlinear integral equations. Moreover, in case of the formation of collaterals, we must handle especially difficult identification tasks of hemodynamically relevant parameters. In the next section we will give an overview of the measurement of the myocardial blood flow. In the section that follows, we will very briefly describe the nature of the inverse problem and the required solution of systems of nonlinear integral equations. We will also point out some open problems.

PET Perfusion Imaging

At present, it is common practice to quantify the perfusion of the myocardium and the myocardial blood flow by PET imaging with specific agents labelled with positron-emitting radionuclides as tracers. We have to distinguish between

- inert freely diffusible tracers, such as $H_2^{15}O$ and
- physiologically retained tracers, such as $[^{13}N]$ ammonia [?, ?] and ^{82}Rb [?].

We will focus here on $[^{13}N]$ ammonia because of its favourable properties. This tracer will to a large extent meet many criteria of an ideal radiotracer for the measurement of MBF, which include

- a fair count-rate capability,
- an almost irreversible trapping in myocardial tissue in direct proportion to myocardial perfusion,
- a rapid clearance from the blood,
- the practical absence of recirculating radiolabeled metabolites, and
- a relatively short physical half-time that facilitates repeated studies.

In PET, an imaging modality with coincidence detection, the scanner counts events between pairs of detectors. Each straight line connecting the centres of two detectors is called a line of response (LOR). The events, the raw data, can be detected in the following two ways:

1. In the so-called histogram mode in which a memory location is assigned to each possible line of response (LOR) and each time a valid event is detected in that LOR, this memory location is incremented by 1.
2. In the so-called list mode in which each event is individually written to file with information comprising the location of the two detector elements that produced the coincidence and the point in time at which the event occurred.

The list mode acquisition approach makes it possible to apply the following advanced PET imaging techniques:

- Dynamic PET imaging
- Cardiac gated PET imaging
- Respiratory gated PET imaging

In particular, a retrospective way of analysis in this mode [?] offers an especially high degree of flexibility. In our measurement efforts of the myocardial blood flow, we must account for the heterogeneity of the perfusion within the myocardium. Assuming a standard coronary anatomy, each branch of the epicardial artery tree has its individual intramyocardial vascular territory which has again a tree-like structure. In the case of formation of stenoses or diffuse narrowing in one (or more) branches of the epicardial artery (arteries), the heterogeneities become more pronounced.

Determination of regional myocardial blood flow with [¹³N] ammonia PET

The regional myocardial blood flow is the amount of volume of blood supplied to the vascular territory of a branch of an epicardial artery per unit of time. The radiotracer [¹³N] ammonia is extracted by the tissue of the myocardium and eventually trapped in the myocardium. The perfusion of the myocardium is defined by as flow of blood into the myocardium per unit mass of tissue. The perfusion image shows the extracted (trapped) amount of radiotracer in the course of time. There exists several modelling approaches for this process of extraction (trapping). A number of experimental investigations have been carried out which show that the perfusion of a supply territory of the myocardium as defined above is a nonlinear function of the myocardial blood flow. To determine the regional myocardial blood flow by means of dynamic perfusion imaging, we have to solve (nonlinear) integral equations [?, ?]. That means mathematically that we need for the

determination of the regional blood flows in the n supply territories of the myocardium a system of n nonlinear integral equations which we can write as:

$$(0.1) \quad \mathbf{y}(\tilde{t}) = \int_0^{T_f} \mathbf{G}(\tilde{t}, \tau, \mathbf{x}(\tau)) d\tau$$

whereby

$$(0.2) \quad \tilde{t} = t - t_a$$

Here,

$$(0.3) \quad \mathbf{y}(\tilde{t}) = (y_1(t), y_2(t), \dots, y_n(t))$$

$$(0.4) \quad \mathbf{x}(\tilde{t}) = (x_1(t), x_2(t), \dots, x_n(t))$$

$$(0.5) \quad \mathbf{G}(\tilde{t}, \tau, \mathbf{x}(\tau)) = (G_1(\tilde{t}, \tau, \mathbf{x}(\tau)), G_2(\tilde{t}, \tau, \mathbf{x}(\tau)), \dots, G_n(\tilde{t}, \tau, \mathbf{x}(\tau)))$$

with the following quantities (variables):

t ... denotes the time after radiotracer bolus

t_a ... arrival time of the radiotracer at the vascular territories

T_f ... duration of scanning process

n ... number of vascular territories of the myocardium

$x_i(t)$ $1 \leq i \leq n$... tracer feeding rate into the i^{th} vascular territory

$y_i(t)$ $1 \leq i \leq n$... activity of the extracted radiotracer in the i^{th} supply territory

$\mathbf{G}(\tilde{t}, \tau, \mathbf{x}(\tau))$ is strongly dependent on the chosen tracer kinetic modelling approach. To attain a sufficiently high accuracy, the number of compartments should be adequate and the decay of the radiotracer taken into account. There still exist several open problems which will be outlined in the talk.

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