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Identification of thyroid gland activity in radioiodine therapy

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ABSTRACT

The Bayesian identification of a linear regression model (called the biphasic model) for time dependence of thyroid gland activity in ^{131}I radioiodine therapy is presented. Prior knowledge is elicited via hard parameter constraints and via the merging of external information from an archive of patient records. This prior regularization is shown to be crucial in the reported context, where data typically comprise only two or three high-noise measurements. The posterior distribution is simulated via a Langevin diffusion algorithm, whose optimization for the thyroid activity application is explained. Excellent patient-specific predictions of thyroid activity are reported. The posterior inference of the patient-specific total radiation dose is computed, allowing the uncertainty of the dose to be quantified in a consistent form. The relevance of this work in clinical practice is explained.

1. Radioiodine therapy for thyroid gland cancer

The thyroid gland [1] is located in the neck. It is an important component of the endocrine system. Specific thyroid cells bind and accumulate free iodine from the blood. Accumulated iodine is used in the synthesis of thyroid hormones. These hormones affect the body in the following ways: metabolic, thermoregulatory, growth and maturation.

While in 1987, when thyroid cancer affected about 5 in every 100 000 people in United States, 80% of them female, in 2009 it was 14 in 100 000 [2]. In therapy, the thyroid is typically removed by surgery. However, it is impossible to remove the organ completely, owing to the proximity of the vocal chords, important arteries and nerves. Hence, in normal clinical practice, these remnants—along with any metastases (which, in common with the thyroid itself, are also iodine-accumulating)—are then destroyed by methods of nuclear medicine (radioiodine therapy).

Radioiodine therapy for thyroid gland cancer [3] exploits the fact that the gland selectively accumulates iodine from the blood. Nuclear decays in unstable (radioactive) ^{131}I release β-particles (electrons) which are absorbed by the thyroid tissue (as well as by other organs). Therapeutic administration of ^{131}I is typically in the activity range of 2–10 GBq,[1] leading to radio-destruction of the thyroid tissue. The accompanying γ-particles (high energy photons) are not absorbed by the tissue and can therefore be detected outside the body. Typically, there is a preliminary diagnostic administration of ^{131}I, at an activity of 70 MBq, in order to assess the mass and disposition of the thyroid remnants, and to provide guidance in the design of the subsequent therapeutic administration.

The ^{131}I *activity*, A_t, of the thyroid, at a time t (days) following administration of ^{131}I, is defined as the mean number of nuclear decays (nuclear decay is a random Poisson-distributed process) occurring in the gland per second at time t. A typical activity curve is illustrated in Fig. 1.

It reveals the characteristic *biphasic* (*i.e.* two-phase) behaviour, comprising the initial *uptake* phase, followed by the *clearance* phase. Note that the time-scale is far shorter than that for radio-destruction and elimination of the tissue by the immune system, which takes 3–6 months. Hence, the clearance is due dominantly to the radioactive decay of ^{131}I and metabolic elimination of the isotope by the thyroid. The key therapeutic quantity of interest is the *absorbed dose*, $\mathcal{D}$, defined as the total energy of the β-particles absorbed per unit mass of the thyroid:

$$\mathcal{D} = \mathcal{S}\xi, \quad \xi = \int_0^{+\infty} A_t \, \mathrm{d}t. \tag{1}$$

Here, $\mathcal{S}$ is a known organ- and isotope-specific constant, provided by the MIRD methodology (Medical Internal Radiation Dose) [4].

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[1] 1 Giga-Becquerel (GBq) corresponds to 10^9 nuclear decays per second.

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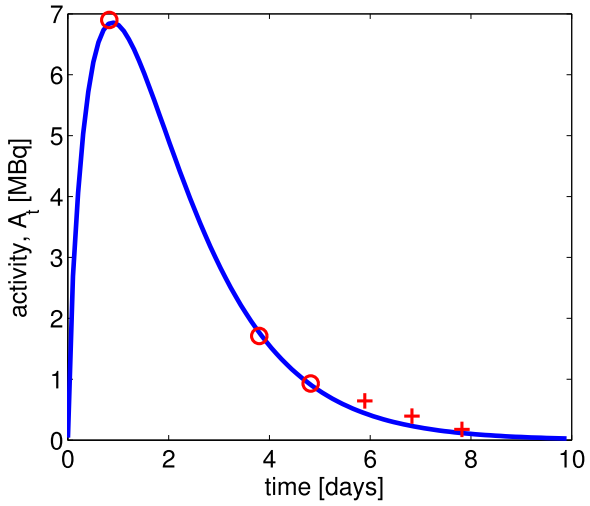

Fig. 1. A typical patient activity curve, A_t, identified using 3 patient measurements (circles). The remaining measurements (crosses) are used to quantify prediction error.

1.1. The measurement process

The β-particles—and hence A_t—cannot be measured directly. However, the associated γ-particles (photons) released by the thyroid during one-second intervals around a measurement time, t, can be detected and counted by a scintillation probe at a specific range and direction [1,5]. A matrix of such counts (*i.e.* a scintigram) is available if an array of such probes—known as a γ-camera—is used. The cumulative count in a Region-of-Interest (ROI) marked on the scintigram by the radiologist is then available at the measurement time, t. In standard radiological practice, the measured background count due to sources other than the thyroid itself is then subtracted, to yield an estimated count, $\hat{n}_t$, of particles from the thyroid. A calibration step then converts $\hat{n}_t$ into an estimate, d_t, of the thyroid activity, A_t, at the measurement time, t. The calibration is achieved using a source of known activity in the same geometrical arrangement as the patient and probe/camera. The calibration-adjusted estimate, d_t (MBq), is called the *measured activity* of the thyroid, and is the conventional statistic computed in standard radioiodine therapeutic practice. Details of this activity estimation procedure are provided in [6]. For a specific patient, the available data, D, are therefore the set of measurement times, t_i, and the associated measured activities, d_{t_i}:

$$D \equiv \{(t_i, d_{t_i})\}_{i=1}^{n},$$

where i is the discrete-time index and n is the number of data recorded for the specific patient.[2]

1.2. The key inference tasks

The ability of thyroid remnants to accumulate iodine depends on the size of the remnants after surgery, the type of carcinoma, the patient's metabolism, the possible presence of metastases, *etc.* Therefore, *patient-specific* inference is of great clinical importance, both at the diagnostic and therapeutic stages.

Therefore, two key inference tasks are addressed in this paper:

1. Patient-specific sequential prediction of measured activity, d_t. There are two uses for these predictions: the first is to validate the parametric model that we will adopt for A_t in Section 2.1; and a second potential use is to provide a tool for quality assurance during logging of measured activities (*i.e.* if the recorded value differs significantly from the predicted one, a warning is generated).
2. Patient-specific inference of ξ and hence the absorbed dose, $\mathcal{D}$ (Section 1). This is the key therapeutic quantity determining the effectiveness of the radioiodine therapy and hence the patient's prognosis. In particular, we wish to quantify the uncertainty in $\mathcal{D}$, since this supports the radiologists in their planning of possible follow-up treatment for the patient. Furthermore, the thyroid acts as a radiation source during radioiodine therapy. β-particles from the thyroid irradiate the blood, while the associated γ-particles irradiate remote organs. Inference of $\mathcal{D}$ allows the radiologist to assess the levels of such irradiation. Note that distributions of non-patient-specific dose have been proposed in the radiation protection literature [7,8]. Recently, the EANM Dosimetry Committee Series, *Standard Operational Procedures for Pre-Therapeutic Dosimetry* [9], provided guidelines on the assessment of patient-specific absorbed dose, but this was non-probabilistic. To our knowledge, no reference, beyond the work reported here, provides a patient-specific probabilistic inference of dose in radioiodine therapy.

A difficult inference regime is implied for the following reasons:

1. for economic reasons, and to avoid possible distress to patients, only a small number, $2 \leq n \lesssim 9$, of non-uniformly sampled measurements, d_{t_i}, are available per patient;
2. these measured activities are subject to considerable uncertainty (noise), due to imprecise calibration of the measurement system and uncertain background radiation levels.

The poor quality, and small quantity, of the available data point to the need for a Bayesian approach to the tasks above, as, successfully, in similar situations, e.g. [10].

1.3. Structure of the paper

In Section 2.1, the biphasic linear regression model for A_t is introduced, for which an elegant Bayesian conjugate framework is available (Section 3). A key benefit of the Bayesian approach in this case is that it provides the opportunity to improve the patient-specific inference using an available database of measured activities for a large population of patients. In Section 4, we use these historic data, as well as known parameter constraints, to construct a suitable prior for the biphasic model parameters. The posterior inference is deduced in Section 5, and problems associated with its evaluation are outlined. Selection and tuning of an appropriate stochastic sampling algorithm for approximation of the exact inference is outlined in Section 6. The resulting activity prediction and dose inference are assessed for a population of actual patients in Section 7. The impact of the work on current clinical practice, and prospects for future work in the area, are discussed in Section 8.

2. Modelling of ^{131}I activity

The uptake and clearance of ^{131}I by the thyroid is a topic in pharmacokinetics (PK), *e.g.* [11]. PK models have been proposed for quantifying the dose associated with inhalation [12] or ingestion [7] of ^{131}I, and for assessing its variability. In [8], the dose variability is evaluated and its distribution is assumed log-normal. In population PK, the individual pharmacokinetic parameters are studied across a patient population, *e.g.* [13]. However, we emphasize that the inference tasks which we defined in the previous Section are patient-specific, and so we do not concern ourselves with population PK models. Reported

[2] The maximum measured activity for each specific patient, which we denote by d_m (we omit any patient-specific index for the time being), can differ by several orders of magnitude within a population of patients, such as the one studied in Section 4.2. This is due to differences in administered activity of ^{131}I, and metabolic variations between patients. For reasons of numerical stability in the Bayesian identification algorithm (Section 3), scaled measured activities, $d_{t_i}/d_m \in (0, 1]$, are modelled for each patient. For notational simplicity, it is these scaled quantities that will be referred to as d_{t_i} in the sequel.