1. Introduction

This repository contains the replication data and code of the study “A model of thyroid disease response to radiotherapy”
It contains the following files, organized in three folders:

1.1. Data files:

data.xls

1.2. Code files:

kinetic_model.m
kinetic_model_Markov.m

1.3. Results files:

Figure3_panels_ABC.mat
Figure3_panels_DEF.mat
Figure4.mat
Figure5.mat
Table1.mat
Table2.mat
Table3.mat

2. Data files

The full dataset used for this study is presented in the data.xls file, in excel format. Three clinical datasets are used with information corresponding to: a) averaged population response of Graves’ hiperthyroidism to radioactive iodine therapy, RAI; b) response of a single patient case of a local recurrence of differentiated thyroid cancer, DTC, to RAI; and, c) response of a single patient case of DTC metastases to RAI. The file provides information about the evolution of thyroid mass/volume, thyroglobulin serum concentration, Tg, and antithyroglobulin autoantibodies serum concentration, TgAb (if present). Information about the treatments includes the number of RAI administrations, and the doses and effective radionuclide half-lifes associated to each 131-I administration.

3. Code

The code consists of two Matlab (The Mathworks, Natick, MA) functions with the implementation of the model of thyroid response to RAI. The first function, kinetic_model.m, is a deterministic implementation of the model, used to fit experimental data from Graves’ disease and differentiated thyroid cancer. The second funcion, kinetic_model_Markov.m is a stochastic implementation of the model, primarily used to quantify the tumor control probability, TCP, associated with the treatment individualization strategies investigated in this work.

4. Results

This folder contains the files with the results corresponding to Figure 3, Figure 4, Figure 5, as well as Table1, Table 2 Table3 of the manuscript, in Matlab format (.mat). The information contained in each file is described in the following sections.

4.1. Figure3_panels_ABC.mat

This Matlab workspace contains the information corresponding to the fit of the model to Graves’ hyperthyroidism average population response data for a single administration RAI treatment. The workspace consists of the following elements:

1) data_graves: 18x3 array with experimental data about the population-averaged response. The first column contains time after treatment (in months). The second column contains information about thyroid volume in ml (rows 1 to 4), total Tg in ng/ml (rows 5 to 11), and TgAb in IU/ml (rows 12 to 18). The third column contains uncertainty values, one standard deviation for the mass (rows 1 to 4), and confidence intervals for Tg and TgAb (rows 5 to 18). This data was taken from [1].

2) dose_graves: Average population absorbed dose to thyroid administered 555 MBq of I-131 to treat Graves’ disease. This value was calculated by using the information provided in [2].

3) halflife_graves: Average population effective half-life of 131-I in thyroids administered 555 MBq of I-131 to treat Graves' disease. This value was calculated by using the information provided in [2].

4) number_of_injections: Number of RAI administrations delivered to the patients.

5) parameters_graves: Vector with the 19 best-fitting parameter values associated to the model for this experiment. See function kinetic_model.m for a description of each parameter (lines 30 to 49 of that file).

6) results: Matlab structure with vectors corresponding to the output of the model: time in days since treatment administration (t); number of undamaged, sublethally damaged, doomed and dead cells (N, Ns, Nd and Ndead, respectively); serum concentration of free and bound Tg in ng/ml (Tg and Tgb, respectively); TgAb serum concentration in IU/ml; treatment dose rate in Gy/day (r); and treatment cumulative dose in Gy (Dcum). The temporal evolution of all these variables was saved from the time of treatment administration (assigned here t=0) with one data point per day.

7) t_before_treatment: Time in days elapsed from the start of the simulation and the treatment administration. If the code kinetic_model.m is run again, this variable should be substracted the quantity t_before_treatment and converted to months to match the experimental data time points.

4.2. Figure3_panels_DEF.mat

This Matlab workspace includes the results associated to the study of interpatient variabilities in the response to RAI of Graves' disease patients. These were calculated simulating the response of 1000 patients with normally distributed parameter values around the best-fitting values and a standard deviation equal to 25%, except for the thyroid mass at the time of treatment, where it was 50%. The workspace contains of the following elements:

1) data_graves: 18x3 array with experimental data from average population response of Grave's disease to RAI. See the structure of this array in the description of data in Figure3_panelsABC.mat.

2) dose_graves: Same variable as that already described in Figure3_panels_ABC.

3) halflife_graves: Same variable as that already described in Figure3_panels_ABC.

4) number_of_injections: Same variable as that already described in Figure3_panels_ABC.

5) parameters_perturbed: 19x1000 array containing 19 parameter values corresponding to 1000 simulated patients. The parameter Nmax was not perturbed but assumed to be equal to 2xN at the time of treatment.

6) results_perturbation: Matlab structure with three 1000x180 arrays corresponding to the main outputs of the model (total number of cells, Nt, total Tg and TgAb) for the 1000 patients simulated. The temporal evolution of the variables is shown at 180 time points (in days) from the the beginning of the treatment. Three other 180x2 arrays (Nt_ci, Tg_ci, and TgAb_ci) show 65% confidence intervals for these variables, with upper and lower values corresponding to each interval in rows 1 and 2, respectively. Vector t shows time in days from the instant of treatment administration.

4.3. Figure4.mat

This Matlab workspace contains the information corresponding to the fit of the model to the response of a patient with a DTC local recurrence treated with RAI with three administrations of 7400 MBq 131-I each. Treatment and patient data corresponding to this patient were taken from [3]. The workspace consists of the following elements:

1) data_local_recurrence: 15x2 array with experimental data. The first column contains data of time after treatment in months. The second column contains information about: total Tg concentration in ng/ml (rows 1 to 6), thyroid mass in grams (rows 7 to 9), and TgAb concentration in IU/ml (rows 10 to 15).

2) dose_local_recurrence: Measured values of absorbed dose to the lesion for each treatment administration.

3) halflife_local_recurrence: Measured effective half-lives of 131-I in the lesion for each treatment administration.

4) number_of_injections: Number of treatment administrations delivered to the patient.

5) parameters_local_recurrence: Vector with the 19 best-fitting parameter values associated to the model for this experiment. See function kinetic_model.m for a description (lines 30 to 49 of this file).

6) results: Matlab structure corresponding to the output of the model: time in days, t; undamaged, sublethally damaged, doomed and dead cells (N, Ns, Nd and Ndead, respectively); concentration of free and bound Tg in ng/ml (Tg and Tgb); TgAb concentration in IU/ml; dose rate in Gy/day, r; and treatment cumulative dose in Gy, Dcum. The temporal evolution

of all these variables was saved from the time of first treatment administration (assigned t=0 here) with one data point per day.

7) t_before_treatment: Same variable as that defined in the description of Figure3_panels_ABC.mat

4.4. Figure5.mat

This Matlab workspace contains the information corresponding to the fit of the model to the response of a patient with three DTC metastasic lesions treated with RAI with two administrations of 7400 MBq each. Treatment and patient data corresponding to this patient was taken from [3]. The workspace consists of of the following elements:

1) data_metastases: 6x4 array with experimental data of the response of the three metastases to treatment. The first column contains data of time after treatment in months. Elements in rows 1 and 2 of the second, third and fourth columns contain information about the mass of metastasis 1, 2 and 3, respectively. Rows 3 to 6 of the second column contain the patient total Tg concentration in ng/ml.

2) dose_metastases: Vector of measured values of absorbed dose to each lesion per RAI administration. Elements 1 to 2, 3 to 4, and 5 to 6 show the doses associated to the first and second administration for metastasis 1, 2 and 3, respectively.

3) halflife_metastases: Effective half-life of 131-I measured for each lesion and treatment administration. Elements 1 to 2, 3 to 4, and 5 to 6 show the half-life associated to the first and second administration for metastasis 1, 2 and 3, respectively.

4) number_of_injections: Number of treatment administrations delivered to the patient.

5) parameters_metastases: Vector with the 19 best-fitting parameter values. See function kinetic_model.m for a description (lines 30-49 of that file). To simulate the evolution of each lesion, the 10^{th} element of the parameters vector must be replaced by the initial number of cells assumed for each lesion. This is calculated as the mass of the lesion in g, (available in data_metastases(1,2), data_metastases(1,3) and data_metastases(1,4), for lesion 1, 2 and 3, respectively) multiplied by a tumor cell density of 10^8 cells/g,

6) results: Matlab structure with vectors corresponding to the output of the model. Some variables are noted with and underscore and a number from 1 to 3, to refer to each lesion: time in days, t; number of undamaged, sublethally damaged, doomed and dead cells (N, Ns, Nd and Ndead, respectively); concentration of free and bound Tg in ng/ml (Tg and Tgb, respectively); treatment dose rate in Gy/day, r; and treatment cumulative dose in Gy, Dcum. The temporal evolution of all these variables was saved from the time of first treatment administration (assigned t=0 here) with one data point per day. The variable t_before_treatment described in Figure3_panels_ABC.mat is saved for each metastasis in this structure.

4.5. Table1.mat

This Matlab workspace includes the results associated to the study of DTC RAI treatment individualization strategy 1, in which the activity administered to each patient is optimized based on the dose delivered to the tumor with a standard treatment. A population of 1000 patients is analyzed, using simulation parameters normally distributed around the best-fitting parameter values calculated for the patient with a DTC local recurrence. The parameter values standard deviation is equal to a 25% of the mean. The workspace contains the following elements:

1) central_parameters: Vector with parameter values providing best fit to the response of the patient with a local recurrence of DTC. See kinetic_model_Markov.m for a description (lines 40-66 of that file).

2) population_parameters: 1000x22 array parameter values normally distributed around central_parameters, used to simulate the population response to RAI for the standard treatment.

3) results_standard_treatment: Matlab structure with the results of treatment simulation corresponding to a standard treatment administration. It contains the temporal evolution of numbers of cells and cumulative dose, using the same notation described for the structure “results” in Figure3_panels_ABC.mat. The variables whose names end with a “_ref”, correspond to the simulation of a patient with central parameter values. The variable control is a vector with values equal to 1 for the patients that achieved tumor control and 0 otherwise. The variable TCP is a vector with the tumor control rates achieved in 5 groups of patients, ordered by ascending level of absorbed dose to the lesion.

4) dose: vector with the cumulative dose delivered by the standard treatment to the tumor for each patient.

5) results_opt_from_dose_delta_10: Matlab structure with the results of treatment simulation for the same population, when patients are administered an individualized treatment based on the dose delivered to the tumor, with a maximum activity boost equal to 10%. It contains the temporal evolution of of numbers of cells and cumulative dose for the population of patients, and control and TCP vectors, equivalent to those saved in the above described structure

"results_standard_treatment". The variable parameters is a 1000x22 array containing simulation input parameter values corresponding to the individualized treatments. All values in this array are equal to those in vector "population_parameters" of this workspace, with the exception of elements in column 20. These values were modified to deliver to each patient personalized activity administration, according to the group each patient was assigned to.

6) results_opt_from_dose_delta_20: Matlab structure with the results of treatment simulation for the same population, when patients are administered an individualized treatment based on the dose delivered to the tumor, with a maximum activity boost equal to 20%.

4.6. Table2.mat

This Matlab workspace includes the results associated to the study of DTC RAI treatment individualization strategy 2, in which the activity administered to each patient is optimized based on the radiosensitivity of tumor cells (evaluated with parameter *b*, associated to sublethal damage). The same population of 1000 simulated patients is analyzed. The workspace contains the following elements:

1) population_parameters: This array is equal to that already described in Table1.mat.

2) results_standard_treatment: This Matlab structure is equal to that already described in Table1.mat, but the variables associated to central parameter values are excluded. Vector TCP contains the tumor control rates achieved in the 5 groups of patients, ordered by ascending level radiosensitivity paramenter b.

4) radiosensitivity_parameter_b: vector with the value of radiosensitivity parameter b for each patient. This vector is also column 6 of the array population_parameters.

6) results_opt_from_b_delta_10: Matlab structure with the results of treatment simulation for the population, when patients are administered an individualized treatment based on the patient radiosensitivity parameter b, with a maximum activity boost equal to 10%. It contains the same variables described in results_opt_from_dose_delta_10 of Table1.mat.

6) results_opt_from_b_delta_20: as above, for a maximum activity boost equal to 20%.

4.7. Table3.mat

This Matlab workspace includes the results for treatment individualization strategy 3, which is a combination of strategies 1 and 2. The population of patients is stratified in 5 groups according to the dose, as in 1, and each of the 5 groups are further split in two groups each (and noted with the letters A and B) attending to the radiosensitivity parameter *b* of each patient. The same population of 1000 simulated patients is analyzed. The workspace contains the following elements:

1) population_ parameters: This array is equal to that already described in Table1.mat

2) results_standard_treatment: This Matlab structure is equal to that already described in Table1.mat, with TCP containing now the tumor control rates achieved in the 10 groups of patients (1A, 1B, 2A, 2B, etc).

3) dose: Vector with the cumulative dose delivered by the standard treatment to the tumor for each patient. This information, as well as the radiosensitivity parameter *b* (values in column 6 of parameters_population), is used to calculate the activity to be administered to each patient in this individualization strategy.

4) patient_stratification: Structure with 10 vectors containing the indices of the patients stratified in 10 groups (from 1A to 5B) attending to the dose and radiosensitivity parameter b.

5) results_opt_from_dose_and_b_delta_10: Matlab structure with the results of treatment simulation for the population, when patients are administered an individualized treatment based on the dose and patient radiosensitivity parameter b. It contains the same variables described in results_opt_from_dose_delta_10 of Table1.mat.

6) results_opt_from_dose_and_b_delta_20: as above, for a maximum activity boost equal to 20%.

References:

1. Traino, A.C. et al. A predictive mathematical model for the calculation of the final mass of Graves' disease thyroid treated with 131I. *Phys Med Biol* 2005, *50*, 2181.
2. Latrofa, F. et al. Effect of thyroglobulin autoantibodies on the metabolic clearance of serum thyroglobulin. *Thyroid* 2018, 28, 288–294.
3. de Keizer, B. et al. Tumour dosimetry and response in patients with metastatic differentiated thyroid cancer using recombinant human thyrotropin before radioiodine therapy. *Eur J Nucl Med Mol ImagingEUR J* 2003, 30, 367–373.