Mathematical models applied to thyroid cancer

Jairo Gomes da Silva¹ · Rafael Martins de Moraes² · Izabel Cristina Rodrigues da Silva³ · Paulo Fernando de Arruda Mancera⁴

Received: 23 January 2019 / Accepted: 7 February 2019 / Published online: 15 February 2019
© International Union for Pure and Applied Biophysics (IUPAB) and Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Thyroid cancer is the most prevalent endocrine neoplasia in the world. The use of mathematical models on the development of tumors has yielded numerous results in this field and modeling with differential equations is present in many papers on cancer. In order to know the use of mathematical models with differential equations or similar in the study of thyroid cancer, studies since 2006 to date was reviewed. Systems with ordinary or partial differential equations were the means most frequently adopted by the authors. The models deal with tumor growth, effective half-life of radioiodine applied after thyroidectomy, the treatment with iodine-131, thyroid volume before thyroidectomy, and others. The variables usually employed in the models includes tumor volume, thyroid volume, amount of iodine, thyroglobulin and thyroxine hormone, radioiodine activity, and physical characteristics such as pressure, density, and displacement of the thyroid molecules. In conclusion, the mathematical models used so far with differential equations approach several aspects of thyroid cancer, including participation in methods of execution or follow-up of treatments. With the development of new models, an increase in the current understanding of the detection, evolution, and treatment of diseases is a step that should be considered.

Keywords Thyroid cancer · Differential equations · Mathematical modeling · Systematic review

Introduction

Thyroid cancer is described as a malignant thyroid gland tumor, and although it accounts for less than 1% of all human cancers, it is the most prevalent endocrine neoplasia in the world (Sipo and Mazzaferi 2010). This malignant neoplasm has several subtypes and the frequency between them varies greatly. Papillary and follicular carcinomas are developed from follicular thyroid cells, and correspond to 80–85% and 10–15% of the cases, respectively, whereas the

medullary thyroid carcinoma representing 3–4%, develops from the C cells. The anaplastic thyroid cancer, 1–2%, is composed of undifferentiated cells, in which the tumor cells do not resemble normal thyroid cells or form follicles. This last subtype consists of thyroid stem cells, which are generally indifferent to radioactive iodine, thyroid stimulating hormone (TSH), and all currently available treatments (Fagin and Wells 2016; Lin 2011; Parameswaran et al. 2010).

Iodine is an essential element for the synthesis of thyroid hormones. After being captured in the bloodstream, it is directed to the glandular cells and thyroid follicles. The rate of iodine uptake by the gland thyroid is influenced by several factors, and one of the most important is the TSH, which triggers this process (Swan et al. 2018). The transport of iodine to the thyroid is mediated by the sodium/iodide symporter (NIS) (Carvalho and Ferreira 2007); this glycoprotein according to Ringel et al. (2001) has markedly reduced expression in thyroid cancerous tissues, which should hamper the concentration of iodine at these sites.

Tumor markers in the blood are not used for the definitive diagnosis of cancer; however, they are useful for screenings and in some situations are essential tools in quantifying

✉ Jairo Gomes da Silva
jairo.silva@bag.ifmt.edu.br

- ¹ Instituto de Biociências, Programa de Pós-Graduação em Biometria, Universidade Estadual Paulista (UNESP), Distrito de Rubião Júnior, Botucatu, SP, 18618–689, Brazil
- ² Faculdade de Ceilândia, Campus Universitário, Programa de Pós-Graduação em Ciências Médicas, Universidade de Brasília (UnB), Ceilândia Sul, DF, 72220275, Brazil
- ³ Faculdade de Ceilândia, Campus Universitário, Universidade de Brasília (UnB), Ceilândia Sul, DF, 72220275, Brazil
- ⁴ Instituto de Biociências, Universidade Estadual Paulista (UNESP), Botucatu, SP, 18618–689, Brazil

responses to therapy or detecting recurrence of the disease (Kumar et al. 2014). Several studies involving predictive models of benign or malignant tumors have been performed based on hormonal dosages and in the presence of markers in patients with suspected cancer or in treatment (Barbolosi et al. 2017; Kolpak et al. 2016; Liu et al. 2018; You et al. 2009).

In general, a mathematical model is a simplified representation of a real-world object. From models, phenomena can be explained and predicted, as the prey-predator model used to study the interaction between some populations. In addition, models can be used in decision-making processes and knowledge communication (Schichl 2004). Mathematical models have long been used to study real phenomena linked to human health. An example of application refers to the work of Danziger and Elmergreen (1956), which develops a model involving the thyroid gland. In this study, the authors defined nonlinear differential equations related to thyrotropin, enzyme, and thyroid hormone concentrations over time. From the model, many concepts about the endocrine system were discussed, such as the production of thyrotropin-releasing hormone (TRH) and hormones, iodine intake, hypothyroidism, estimation of parameters, and others.

According to Barbolosi et al. (2016), the area of cancer research in general has experienced the possibility of innovation in techniques or treatments personalized from mathematical models. As example, in thyroid cancer, some models have been published with the objective of evaluating the efficiency of procedures and determining prognostic factors for differentiated carcinomas. From these models, it is possible to know the predictability of results and, consequently, a change in procedures over the course of treatment if necessary (Barbolosi et al. 2017; Yildirim 2005).

The approach of clinical oncology in terms of mathematical modeling is revised in Park (2016); in this review article, the author presents several texts published with mathematical models about cancer. The different models deal with aspects of the disease such as tumor size, which discusses the use of analytical or differential equations, models for tumor markers, biomarkers, adverse effects after treatments, and progression-free survival.

Faced with the complexity of cancer, mathematical models are currently seen as a valuable research tool, and the use of differential equations highlight as the main means of study from several papers (Abduvaliev et al. 2015; Hori and Gambhir 2011; Park 2016; Jackson 2004; Rodrigues et al. 2016). Ordinary differential equations (ODE) contain functions of one variable, commonly time, and derivatives from this same variable, whereas partial differential equations (PDE) have functions with two or more variables and their partial derivatives. When applied

to biology, ordinary and partial differential equations generally measure changes in populations or concentrations of substances in the time dimension, or space and time, respectively (Boyce and DiPrima 2012; Hirsh et al. 2004).

Thus, motivated by the fact that experiments guide theories and theories foster experiments (Komarova 2005), this systematic review seeks to provide a current assessment of the use of mathematical models involving mainly differential equations in the study of tumors and development and treatment of thyroid cancer.

Material and methods

Search strategy

This systematic review was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) methodology (Moher et al. 2009). The literature search was made through the Web of Science, PubMed, Scopus, Cochrane Library, Embase and LILACS databases, and in the Google Scholar references search site. Different bibliographic sources were consulted because besides to mathematical models of biological phenomena being published in health journals; they are also available in journals of applied mathematics, or the like. The cited collection occurred in March 2018. Any publications that had some relation between mathematical models and the thyroid gland were surveyed. The search terms used were as follows: “mathematical modeling” “thyroid,” “mathematical model” “thyroid,” “mathematical model” “iodine,” “mathematical model” “thyroidectomy,” “mathematical model” “therapeutic nuclear thyroid,” “differential equations” “thyroidectomy.” The expressions “mathematical modeling of thyroid” and “mathematical model of thyroid” were used only on Google Scholar for refinement in the search. In the Embase database the search was performed from the keywords “Applied Mathematical Modeling” and “thyroid cancer.” The lists of references provided by Google Scholar were in general very numerous, and therefore, the collection of articles occurred only among the first 40 suggested texts for each search term. For management of the papers and verification of duplicates the Mendeley software was used. As for the language, the literature collected was in English, Spanish, or Portuguese.

Inclusion and exclusion criteria

The first filter used to select a work was that it should approach the thyroid gland using a mathematical model. Inclusion criteria were as follows: (1) the study should address some characteristic of thyroid cancer; (2) the study should present some mathematical model applied

to the identification, evolution, treatment, or follow-up of the disease; (3) the mathematical model in the study should preferably include ODEs or PDEs systems. Studies were excluded when they were related to other diseases of thyroid, such as Graves' disease, hyperthyroidism and hypothyroidism, and the like. The selection process consisted primarily of reading the title and abstract. In cases where this process was still in doubt as to the fulfillment of the inclusion or exclusion criteria, the text was read in its entirety. Although criterion (3) is considered central to the scope of this review, two papers involving nondifferential equations were accepted. A complete diagram of the collection and selection of articles is presented in Fig. 1.

Data extraction

The data and the main features for analysis and comparison between the selected studies were independently extracted in accordance with the inclusion and exclusion criteria. For each paper, the following information were collected: authors, study title, the year of publication, if some biological sample was used, type of model, main subject, and variables used in mathematical models.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Fig. 1 Diagram of collection and selection of articles. Identification of databases or sites and number of works found, duplicated, and selected

Results

The literature search found articles published between 2006 and 2017. Four hundred twenty-four articles were collected with a total of 114 duplicates. At the end of the selection process, seven articles were considered according to the established criteria. Although some diseases present a much greater number of papers with ODE or PDE than thyroid cancer, the articles found deal with the disease considering several stages of its development. However, the number of published articles focusing on thyroid cancer can be considered scarce.

From the search, it was noticed that the presence of mathematical models in the study of the thyroid gland is quite common, articles with modeling on diseases or processes such as thyroid function, hypothalamus-pituitary-thyroid axis, Graves' disease, hypothyroidism or hyperthyroidism, goiters are frequent (Abduvaliev et al. 2015; Danziger and Elmergreen 1956; Goede et al. 2014; Hoermann et al. 2013; Langenstein et al. 2016; Leow 2016).

As for the articles that were included in the systematic review, an overview of each is given as follows. In Lubitz et al. (2016), there is a mathematical approach using an ODE model with logistic growth for both benign and malignant thyroid tumors. In the text are modeled some characteristics as tumor volume over time, development rate, and detection rate among others. Moreover, a carrying capacity for the tumor in the final phase of the anomaly is proposed. From the parameter estimation, the researchers approached data about the number of cases of onset, initial growth, and development of thyroid nodules and cancer in the US population. In addition, the research aims to provide a framework for assessing the adequacy, efficacy, and cost-effectiveness of papillary thyroid cancer treatment.

In Ruggieri et al. (2008) are discussed some techniques to estimate the preoperative thyroid volume in patients undergoing to total thyroidectomy and is presented a novel mathematical equation to obtain this value. The validation of the results is made by comparing the estimated data with postsurgical tumor volume. From the study, it is intended to provide a more accurate way to measure thyroid gland than the use of two-dimensional ultrasonography. The developed mathematical model is a linear equation. The paper compose this review because of the general aspect of mathematical modeling in a process also related to the treatment of thyroid cancer.

In order to model the diffusion of a thyroid nodule, in Kolpak et al. (2016), the authors present two models of differential equations: an ODE model on the normal functioning of the thyroid, and a PDE model on the diffusive process of a nodule. Both models act on thyroid follicles, in which they consider reactions such as uptake and binding of iodine to thyroglobulin, formation, and accumulation

of thyroxine (T4) hormone. According to the authors, abnormal growth of thyroid gland may be accompanied by various disorders in some of its functions, such as, iodine uptake, hormone production, control over the transfer of hormones to the bloodstream, and so on. The article works with tumor markers and assumes as variables the concentrations of iodine, thyroglobulin, T4 hormone, and concentration of tumor cells. The system that deals with nodules considers that tumor cells evolve spatially and temporally.

The detection of thyroid cancer nodules by means of PDE models that simulate the propagation of sound in order to detect the presence of tumors by measuring the frequency of resonances is analyzed in Gavrioloia and Gavrioloia (2010). In this work, among the ways of investigating the thyroid from the dynamic point-of-view, the article addresses the use of acoustic. According to the authors, it is possible to verify the existence of thyroid nodules by measuring the lowest resonance frequency, when the reflected signal amplitude is minimal. It is worth mentioning that the method is non-invasive and brings the possibility of early treatment for the disease, including the chance of thermal treatments to the nodules.

The use of drugs in the treatment of thyroid cancer should be analyzed by efficiency in the healing process and side effects. In general, adverse effects related to drug toxicity depend on parameters, such as dose, routine, and period of medication administration (Carneiro et al. 2015). In Traino and Di Martino (2006), the authors discuss from some mathematical models the quantities of ^{131}I for the ablation of thyroid remnants postsurgery or metastasis. The ablation process is aimed to eliminate cancer residues, possibly present in thyroid bed or other body organs, and thereby enabling the use of thyroglobulin (Tg) as a tumor marker in order to evaluate the success of the treatment over time. The model is formulated so that the amount of remaining cells is minimal according to a threshold value, and enables the individual calculation of the optimum therapeutic activity to be administered to the patient.

An ODE model representing different levels of iodine variations in five compartments of the human body is presented in Chen et al. (2007). According to the authors, the evaluation of iodine effective half-life is essential in patients following ablation of thyroid remnants due to dose prediction and cancer risk assessment. Through the equations model and experimental data collected from follow-up to five patients undergoing to ablation of the thyroid gland and scan using a gamma camera, the study verifies how the effective half-life of iodine varies in selected cases.

Lastly, the article of Barbolosi et al. (2017) brings a mathematical model of ODE and presents an algorithm for estimation of parameters according to individualized

data from patients who underwent thyroidectomy, and subsequently developed metastasis. The strength of the model is to be able to verify the effectiveness of iodine 131 (^{131}I) treatment over therapeutic dose applications, and this is done from the prediction of relapse based on partial data thyroglobulin levels and tumor doubling time in each patient. The results of the model consist in the establishment of criteria for patients submitted to radioiodine therapy so that they can be classified as responders or not while the treatment is in progress. As a result, the research findings provide the possibility of perform the treatment follow-up in a personalized way.

The main information about the mathematical models and each selected work are summarized in Table 1.

Discussion

A challenging aspect of the use of mathematical models concerns the estimation of parameters and in some papers of this review the realization of this process is observed (Barbolosi et al. 2017; Chen et al. 2007; Lubitz et al. 2016). However, for accomplishing this task, a database and appropriate methods should be used. In Kolpak et al. (2016), some parameters have their values taken from published literature, while others are assumed to correspond reasonably to the biological processes involved. A second fundamental characteristic related to modeling concerns the quantity and quality of the variables used. In general, the choice of the set of variables refers to the aspect to be elucidated and to the degree of complexity or realism to be obtained with the model (Park 2016).

To understand the variables used in the articles that compose this review, it is necessary to know the main processes on the functioning of the thyroid gland and in the stages of development and treatment of cancer. The hypothalamus-pituitary-thyroid (HPT) axis is a feedback system that represents a synthesis of the functioning of this gland in the human body. When the hormones produced by the thyroid are in low amounts, the hypothalamus takes cognizance through negative feedback and begins to secrete TRH, which plays the role of stimulating the production of TSH (Degon et al. 2008). The pituitary gland is the organ responsible for the production of TSH after receiving the stimulus. Once this hormone enters the bloodstream, it reaches the thyroid, triggering the processes of iodine uptake, synthesis of thyroglobulin, and release into the blood of hormones triiodothyronine (T3) and T4 that were stored.

The two major hormones secreted by the thyroid are T4 and T3, which are formed within the thyroglobulin molecule in a quantitative T4:T3 ratio of almost 15:1 (Leow 2016; Hoermann et al. 2013). On the relationship between serum

Table 1 Comparison of mathematical models on thyroid cancer or related events

Author	Study	Year	Biological sample	Model	Topic	Variables
(Lubitz et al. 2016)	The thyroid cancer policy model: a mathematical simulation model of papillary thyroid carcinoma in the US population	2017	Yes	ODE	Tumor growth	Tumor volume
(Ruggieri et al. 2008)	The estimation of the thyroid volume before surgery: an important prerequisite for minimally invasive thyroidectomy	2008	Yes	Linear model	Thyroid volume	Thyroid volume estimation via two-dimensional ultrasound
(Kolpak et al. 2016)	A mathematical model of thyroid tumor	2016	No	ODE and PDE	Tumor growth	Iodo, Tg, T4 and Tumors cells
(Gavriloaia and Gavriloaia 2010)	Multispectral acoustic investigation of a thyroid geometrical model	2010	No	PDE	Nodule detection	Pressure, density and displacement of the thyroid molecules
(Traino and Di Martino 2006)	A dosimetric algorithm for patient-specific ^{131}I therapy of thyroid cancer based on a prescribed target-mass reduction	2006	No	Linear quadratic	Optimum absorbed dose ^{131}I calculation	Mass of the thyroid tissue. The target absorbed dose
(Chen et al. 2007)	Effective half-life of iodine for five thyroidectomy patients using an in vivo gamma camera approach	2007	Yes	ODE	Evaluation of the T_{eff} of iodine for thyroidectomy	Quantities of ^{131}I in four compartments of the human body
(Barbolosi et al. 2017)	Modeling therapeutic response to radioiodine in metastatic thyroid cancer: a proof-of-concept study for individualized medicine	2017	Yes	ODE	Efficiency of radiiodine treatment in thyroid cancer	Radiiodine activity Tumor cells Thyroglobulin

T4 and serum TSH, some studies suggest that this is not log-linear (Hadlow et al. 2013; Hoermann et al. 2010).

Basically, the development of thyroid cancer occurs through the sequential accumulation of changes in the genes leading to the stimulation of cell proliferation, invasion, and other carcinogenic properties (Dralle et al. 2015; Efanov et al. 2017; Lin 2011). According to Dralle et al. (2015), processes of evolution and dedifferentiation of thyroid cancer are more frequent in tumors with mutations in the BRAF and RAS genes, and naturally involve the accumulation of additional genetic mutations.

Each malignant tumor in the thyroid gland should receive a specific treatment according to its subtype, the degree of mutation and its stage of evolution. As an example, it may be mentioned that the effectiveness of radioiodine therapy in metastases generally produces excellent prognostics when they are avid for iodine (Barbolosi et al. 2017). In this regard, in many situations, it is common and indicated to administer drugs to alter hormone levels in patients before

treatments, in order to optimize responses to therapies (Bonnema and Hegedüs 2012; Oh et al. 2017).

The choice of variables is a decisive step in the modeling process; this phase influences the design of the data that will be used and the main results to be obtained. In the papers that form this review, the following variables were considered: tumor volume or thyroid volume, amount of iodine, thyroglobulin and T4 hormone, radioiodine activity, tumor cells, and physical characteristics such as pressure, density, and displacement of the thyroid molecules. However, mathematical models that directly involve genes or immune system were not found.

In this review, several types of mathematical models on thyroid cancer were studied and the ODEs were the means most frequently adopted by the authors. From this tool, aspects such as tumor growth (Lubitz et al. 2016; Kolpak et al. 2016); effective half-life of radioiodine applied after thyroidectomy (Chen et al. 2007); and the efficiency of the treatment with ^{131}I in metastatic thyroid cancers (Barbolosi

et al. 2017) could be addressed. Otherwise, the PDEs were considered in the study of the diffusive process of tumors (Kolpak et al. 2016) and detection of nodules, with a suggestion of thermal treatment from the results obtained (Gavriloaia and Gavriloaia 2010).

Linear or linear-quadratic analytical equations were used in two works: Ruggieri et al. (2008), in which a method was proposed to obtain thyroid volume before thyroidectomy, and Traino and Di Martino (2006), where the optimum dose of ^{131}I in order to achieve maximum elimination of remaining thyroid tissue after removal of the gland was estimated.

On the subtypes of modeled cancers, the papers (Barbolosi et al. 2017; Lubitz et al. 2016; Chen et al. 2007) focused on papillary thyroid cancer, Ruggieri et al. (2008) and Gavriloaia and Gavriloaia (2010) dealt with thyroid cancer in general, and Traino and Di Martino (2006) refers to differentiated cancer. In Kolpak et al. (2016), since the main model predicts a cessation in iodine uptake, and consequently, the nonproduction of thyroglobulin and T4 hormone by the thyroid cells, this work may be related to anaplastic thyroid cancer. Therefore, although there are few works involving mathematical models about thyroid cancer, those published until May 2018 address aspects of almost all subtypes of thyroid cancer. In addition, they discuss distinct stages of the disease and leave open the need for more work with the use of databases and investigations on the influence of genes, immune system, and tumor markers in future research.

Conclusions

According to the articles reviewed, mathematical models can be used to aid in the detection of abnormalities in screenings and predict responses, efficacy, and toxicity during treatment planning or adaptation in patients with thyroid cancer. In particularly, the following aspects related to this disease were verified: thyroid volume and tumor growth, nodule detection, evaluation of the effective half-life of iodine 131 in patients who undergo thyroidectomy, besides the effectiveness of radioiodine in patients with metastases. The mathematical models found used ODE, PDE, linear, and linear-quadratic-type equations. Compared to other types of cancer, the number of models found was reasonable, however, capable of generating important results on the main aspects of the disease. Considering the increasing number of nodules detected each year and the recent discoveries about treatments and evolution of thyroid carcinomas, the development of new mathematical models in thyroid cancer is an promising contribution, and knowledge of current models should be an important step in this process.

Author's contributions All authors approved the final manuscript and actively participated in its accomplishment.

Compliance with Ethical Standards

Conflict of interests Jairo Gomes da Silva declares that he has no conflict of interest. Rafael Martins de Moraes declares that he has no conflict of interest. Izabel Cristina Rodrigues da Silva declares that she has no conflict of interest. Paulo Fernando de Arruda Mancera declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Abduvaliev A, Saydalieva M, Hidirova M, Gildieva M (2015) Mathematical modeling of the thyroid regulatory mechanisms. *Am J Med Sci Med* 3(3):28–32
- Barbolosi D, Ciccolini J, Lacarelle B, Barlési F, André N (2016) Computational oncology—mathematical modelling of drug regimens for precision medicine. *Nat Rev Clin Oncol* 13:242–54
- Barbolosi D, Summer I, Meille C, Serre R, Kelly A, Zerdoud S, Bournaud C, Schwartz C, Toubreau M, Toubert ME, Keller I, Taieb D (2017) Modeling therapeutic response to radioiodine in metastatic thyroid cancer: a proof-of-concept study for individualized medicine. *Oncotarget* 8(24):39167–76
- Bonnema SJ, Hegedüs L (2012) Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocr Rev* 33(6):920–80
- Boyce WE, DiPrima R (2012) Elementary differential equations and boundary value problems. Wiley, USA
- Carneiro MLB, Lopes CAP, Miranda-Vilela AL, Joanitti GA, Silva ICR, Mortari MR, Souza AR, Bão BN (2015) Acute and subchronic toxicity of the antitumor agent rhodium (ii) citrate in Balb/c mice after intraperitoneal administration. *Toxicol Rep* 2:1086–100
- Carvalho DP, Ferreira ACF (2007) The importance of sodium/iodide symporter (NIS) for thyroid cancer management. *Arq Bras Endocrinol Metab* 51(5):672–82
- Chen CY, Chang PJ, Changlai SP, Pan LK (2007) Effective half life of iodine for five thyroidectomy patients using an in vivo gamma camera approach. *J Radiat Res* 48(6):485–93
- Danziger L, Elmergreen GL (1956) The thyroid-pituitary homeostatic mechanism. *Springer* 18(1):1–13
- Degon M, Chipkin SR, Hollot CV, Zoeller RT, Chait Y (2008) A computational model of the human thyroid. *Math Biosci* 212:22–53
- Dralle H, Machens A, Basa J, Fatourehchi V, Franceschi S, Hay ID, Nikiforov YE, Pacini F, Pasieka JL, Sherman SI (2015) Follicular cell-derived thyroid cancer. *Nat Rev Dis Primers* 1 (15077). <https://www.nature.com/articles/nrdp201577>
- Efanov AA, Brenner AV, Bogdanova TI, Kelly LM, Liu P, Little MP, Wald AI, Hatch M, Zurnadzy LY, Nikiforova MN, Drozdovitch V, Leeman-Neill R, Mabuchi K, Tronko MD, Chanock SJ, Nikiforov YE (2017) Investigation of the relationship between radiation dose and gene mutations and fusions in post-chernobyl thyroid cancer. *J Natl Cancer Inst* 110(4):371–8
- Fagin JA, Wells SA (2016) Biologic and clinical perspectives on thyroid cancer. *N Engl J Med* 375:1054–67

- Gavriloaia GV, Gavriloaia MR (2010) Multispectral acoustic investigation of a thyroid geometrical model. In: Proceedings of IEEE engineering in medicine and biology society (EMBC), August 2010, Argentina Annual International Conference of the IEEE, pp 585–588
- Goede SL, Leow MKS, Smit JWA, Klein HH, Dietrich JW (2014) Hypothalamus-pituitary-thyroid feedback control: implications of mathematical modeling and consequences for thyrotropin (TSH) and free thyroxine (FT4) reference ranges. *Bull Math Biol* 76:1270–87
- Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EM, Walsh JP (2013) The relationship between TSH and free T4 in a large population is complex, non-linear and differs by age and gender. *J Clin Endocrinol Metab* 98(7):2936–43
- Hirsh MW, Smale S, Devaney RL (2004) Differential equations, dynamical systems and an introduction to chaos. Elsevier, USA
- Hoermann R, Eckl W, Hoermann C, Larisch R (2010) Complex relationship between free thyroxine and tsh in the regulation of thyroid function. *Eur J Endocrinol* 162:1123–29
- Hoermann R, Midgley JEM, Larisch R, Dietrich JW (2013) Is pituitary TSH an adequate measure of thyroid hormone-controlled homeostasis during thyroxine treatment? *Eur J endocrinol* 168:271–80
- Hori SS, Gambhir SS (2011) Mathematical model identifies blood biomarker-based early cancer detection strategies and limitations. *Sci Transl Med* 3:109–16
- Jackson TL (2004) A mathematical model of prostate tumor growth and androgen-independent relapse. *Disc Cont Dyn Sys B* 4:187–201
- Kolpak EP, Frantsuzova IS, Alexandrovich KS (2016) A mathematical model of thyroid tumor. *Glob J Pure Appl Math* 12:55–66
- Komarova NL (2005) Mathematical modeling of tumorigenesis: mission possible. *Curr Opin Oncol* 17:39–43
- Kumar V, Abbas AK, Aster JC (2014) Robbins and Cotran pathologic basis of diseases. Elsevier, Philadelphia
- Langenstein C, Schork D, Badenhop K, Herrmann E (2016) Relapse prediction in Graves' disease: towards mathematical modeling of clinical, immune and genetic markers. *Rev Endocr Metab Disord* 17:571–81
- Leow MKS (2016) A review of the phenomenon of hysteresis in the hypothalamus-pituitary-thyroid axis. *Front Endocrinol* 7(64). <https://doi.org/10.3389/fendo.2016.00064>
- Lin RY (2011) Thyroid cancer stem cells. *Nat Rev Endocrinol* 7:609–16
- Liu J, Zheng D, Li Q, Tang X, Luo Z, Yuan Z, Gao L, Zhao J (2018) A predictive model of thyroid malignancy using clinical, biochemical and sonographic parameters for patients in a multi-center setting. *BMC Endocr Disord* 18:17
- Lubitz C, Ali A, Zhan T, Heberle C, White C, Ito Y, Miyauchi A, Gazelle GS, Kong CY, Hur C (2016) The thyroid cancer policy model: a mathematical simulation model of papillary thyroid carcinoma in the U.S. population. *PLoS ONE* 12(5):e0177068. <https://doi.org/10.1371/journal.pone.0177068>
- Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *PLoS Med* 6(7):e1000097
- Oh JM, Lee HW, Kalimuthu S, Gangadaran P, Baek SH, Han MH, Hong CM, Jeong SY, Lee SW, Lee J, Ahn BC (2017) Development of an athyroid mouse model using ¹³¹I ablation after preparation with a low-iodine diet. *Sci Rep* 7:13284
- Parameswaran R, Brooks S, Sadler GP (2010) Molecular pathogenesis of follicular cell derived thyroid cancers. *Int J Surg* 8:186–93
- Park K (2016) A review of modeling approaches to predict drug response in clinical oncology. *Yonsei Med J* 58:1–8
- Ringel MD, Anderson J, Souza SL, Burch HB, Tambascia M, Shriver CD, Tuttle RM (2001) Expression of the sodium iodide symporter and thyroglobulin genes are reduced in papillary thyroid cancer. *Mod Pathol* 14(4):289–96
- Rodrigues DS, Mancera PFA, Suani STR (2016) Understanding the antiangiogenic effect of metronomic chemotherapy through a simple mathematical model. *Physica A* 464:251–66
- Ruggieri M, Fumarola A, Straniero A, Maiuolo A, Coletta I, Veltri A, Di Fiore A, Trimboli P, Gargiulo P, Genderini M, D'Armiento M (2008) The estimation of the thyroid volume before surgery: an important prerequisite for minimally invasive thyroidectomy. *Langenbecks Arch Surg* 393:721–24
- Schichl H (2004) Models and the history of modeling. In: Kallrath J (ed) Modeling languages in mathematical optimization, vol 88. Springer, Boston, pp 25–36
- Sipo JA, Mazzaferi EL (2010) Thyroid cancer epidemiology and prognostic variables. *Clin Oncol* 22:395–404
- Swan KZ, Nielsen VE, Godballe C, Thrane JF, Mortensen MR, Schytte S, Pedersen HB, Christiansen P, Bonnema SJ (2018) Is serum TSH a biomarker of thyroid carcinoma in patients residing in a mildly iodine-deficient area? *Endocr* 61(2):308–16
- Traino AC, Di Martino FA (2006) Dosimetric algorithm for patient-specific ¹³¹I therapy of thyroid cancer based on a prescribed target-mass reduction. *Phys Med Biol* 51:6449–56
- Yildirim E (2005) A model for predicting outcomes in patients with differentiated thyroid cancer and model performance in comparison with other classification systems. *J Am Coll Surg* 200(3):378–92
- You B, Girard P, Paparel P, Freyer G, Ruffion A, Charrié A, Hénin E, Tod M, Perrin P (2009) Prognostic value of modeled PSA clearance on biochemical relapse free survival after radical prostatectomy. *Prostate* 69:1325–33