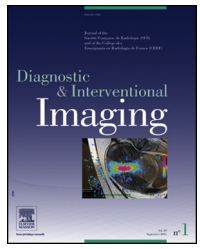
Diagnostic and Interventional Imaging (2013) **94**, 593—600



REVIEW / *Technical*

In vivo mathematical modeling of tumor growth from imaging data: Soon to come in the future?

F. Cornelis[a,b,*,c], **O. Saut**[d], **P. Cumsille**[a], **D. Lombardi**[a], **A. Iollo**[a], **J. Palussiere**[c], **T. Colin**[a]

[a] *Bordeaux University, IMB, UMR 5251, 33400 Talence, France*
[b] *Department of Adult Diagnostic and Interventional Imaging, Pellegrin Hospital, Bordeaux University Hospitals, place Amélie-Raba-Léon, 33076 Bordeaux, France*
[c] *Department de Radiology, Bergonié Institute, 229, cours de l'Argonne, 33076 Bordeaux, France*
[d] *CNRS, IMB, UMR 5251, 33400 Talence, France*

KEYWORDS
Modeling;
Tumor;
Imaging;
Evaluation

Abstract The future challenges in oncology imaging are to assess the response to treatment even earlier. As an addition to functional imaging, mathematical modeling based on the imaging is an alternative, cross-disciplinary area of development. Modeling was developed in oncology not only in order to understand and predict tumor growth, but also to anticipate the effects of targeted and untargeted therapies. A very wide range of these models exist, involving many stages in the progression of tumors. Few models, however, have been proposed to reproduce in vivo tumor growth because of the complexity of the mechanisms involved. Morphological imaging combined with ''spatial'' models appears to perform well although functioning imaging could still provide further information on metabolism and the micro-architecture. The combination of imaging and modeling can resolve complex problems and describe many facets of tumor growth or response to treatment. It is now possible to consider its clinical use in the medium term. This review describes the basic principles of mathematical modeling and describes the advantages, limitations and future prospects for this in vivo approach based on imaging data.

Nowadays, imaging lies at the heart of patient management, particularly in oncology. Apart from the time when a disease is diagnosed, the different imaging methods are used to assess the effectiveness of both local (surgery, radiotherapy, heat ablation) and systemic (chemotherapy, targeted therapy) treatments during follow-up. The protocols usually recommend assessment criteria such as the RECIST, WHO or CHOI, although these are less than perfect [1].

* Corresponding author.
E-mail address: francois.cornelis@chu-bordeaux.fr (F. Cornelis).

2211-5684/$ — see front matter
http://dx.doi.org/10.1016/j.diii.2013.03.001

Nevertheless, the future challenges for imaging are to assess response to treatment and to change treatment even earlier, making it increasingly targeted and appropriate and as soon as possible if necessary. This approach can optimize treatment and reduce costs. At present it is based mostly on functional imaging, which is expanding greatly [2]. This aspect of imaging provides considerable information about cellular activity (PET), nutrient consumption [3], angiogenesis and capillary permeability (perfusion MRI) [4] and also tissue micro-architecture (diffusion MRI) [2], to name a few examples. In this situation, modeling may be an alternative, cross-disciplinary area of development.

Mathematical modeling has been developed in oncology in order both to understand and predict tumor growth and to anticipate the effects of targeted or non-targeted therapies (e.g. the anti-angiogenics). There is a very wide range of these models involving many stages in tumor progression. They can, for example, help to understand the influence of genetic regulation [5] or predict an effect, which has been observed experimentally [6].

In most of these cases, however, the models are better suited for in vitro studies as they are often focused on a small cell contingent, progression of which is more straightforward to observe. The problem in vivo becomes more complex as it needs to take account of an entire tumor containing a large number of cells and therefore mechanisms to be elucidated. In addition, unlike in vitro studies, the amount of information available without modeling a tumor in vivo is very little as it is ''swamped'' by the large number of cells and therefore also with signals. It would appear essential therefore to develop appropriate means to collect the maximum of information in order to optimize these models.

Apart from biopsies, which provide microscopic information, albeit from limited samples, imaging examinations have become essential as they allow repeated, non-invasive information to be recovered over time. The size (or volume), shape, site and uptake after contrast injection are relatively easy parameters to obtain whereas micro-architecture or perfusion data are still difficult and depend on the target organ. The information obtained can be used to refine models and ultimately be applied to clinical practice.

This review explains the basic principles of mathematical modeling and describes the advantages, limitations and future prospect of this in vivo approach based on imaging data.

Concepts of modeling tumor growth

Entirely schematically, several successive stages can be identified in the growth of a solid tumor due to deregulation of cell division: initial avascular growth, angiogenesis, and finally metastatic spread.

During the avascular growth phase, the tumor (according to the monoclonal hypothesis of cancer, the tumor initially consists of a single abnormal cell) grows within the limits of its local environment in a characteristic ''layer'' model [7]. Nutrient supply to the centre of the tumor is inadequate and necrosis may occur. A layer of quiescent cells, which survive without dividing with limited slow metabolism, is found between the two layers. According to this type of model, tumor growth is then severely restricted and in order to continue growing it needs to find additional nutrient sources. The tumor then enters its second stage of growth, the vascular phase. As a result of hypoxic pressure some phenotypes can be favored (through Darwinian selection). Some cells then produce signals (such as VEGF), which encourage the body to vascularize the tumor and therefore provide it with new nutrients (this is the process of angiogenesis). It is important to be aware of this stage for several reasons. Once it is vascularized the tumor can reach significantly far larger sizes than in the previous stage and then be visible on imaging. Finally, vascular fragmentation leads to metastatic spread.

It is therefore not difficult to understand that because of the complexity of the processes involved in all of these stages, mathematical models are to a large extent phenomenologic and extremely simplified compared to what happens in biological reality. Two main types of modeling can be distinguished, which depend on whether or not the tumor is integrated into its neighbouring space.

Non-spatial models calculate the change in one or more major appropriate scales in order to monitor tumor growth. Classic examples are models based on ordinal differential equations (ODE), which describe the change in volume or radius of the tumor. These do not take account of the tumor environment or its interactions but just of measurable dimensions [8]. These models are, however, too simple to provide useful, reliable, reproducible information about the tumor from the phenomenologic change in its volume, which varies at random between different tumors and patients. They may, however, be made more complex to incorporate several compartments (depending on the cell cycle) or to take account of different processes such as angiogenesis.

Conversely, the spatial model takes into account of the tumor environment. Several methods have been proposed to model tumor growth in this way [9,10]. One involves describing the progression of cells individually [11] and produces ''discrete'' automated cell models [12] or agent models [13]. These relatively simple models are very effective in simulating in vitro growth to describe microscopic effects and link them to the molecular level [14]. However, it does not seem currently possible to model an entire complex of cells in its environment, i.e. an entire tumor, as this is too difficult and technically complex.

Another approach to spatial modeling involves working on several cells or population of cells at the same time and therefore describing the change in cell densities (or the boundaries of tumors for example). This allows tumors of realistic size to be studied and takes account of macroscopic effects (for example, interactions between cells and an extracellular membrane or cellular adhesion) using models inspired from continuous medium mechanics [15]. The tissue studied is then treated as a continuum governed by a behavior law in the medium. It is thus straightforward to take account of an extensive complex environment although it is difficult to take all of the independent and non-independent microscopic effects [15] into account. Some models do however, take angiogenesis into account [14,16], and others pay more attention to chemotaxis [17]. In parallel, in terms of tissue description, both mono- and multiphase cell population interaction models have been studied [18,19]. Cell cycle modeling has also been studied [20], with a view to

optimizing treatment [21—23]. These spatial models can therefore incorporate a 2 (or more) phase cell cycle, one of proliferating cells and the other of quiescent cells, and also take account of a necrosis phase. In addition, oxygen diffusion, angiogenesis and interactions with membranes [24] or neighbouring tissues can also be taken into account.

These spatial models have the advantage of incorporating far more biological knowledge and have several benefits, which justify their use. They are said to reproduce realistic behavior, with the desired purpose, and can also test cell interaction hypotheses [25] in an entity such as a tumor. They are often, however, very complex, as they contain experimentally inaccessible parameters and are not specific for a patient, as parameters vary greatly in different situations. They are not therefore suitable for clinical use.

In order to adapt the spatial models to each disease and patient, they therefore need to be simplified and calibrated with clinical data which can be obtained for example by imaging in order to estimate the different parameters in the equations and therefore obtain quantitative results.

Spatial mathematical models based on imaging

All of the information available from morphological imaging can be used in mathematical modeling. Dimensions, volume, density and intensity are those which are used most often. Changes over time provide additional information. The use of functional imaging data is still in the developmental phase and the choice of a model will also depend on the temporal distribution of the available data, as statistical models require more data than determinist models to start the modeling process.

Statistical models

These models require a large amount of initial data. Information obtained from imaging investigations often exhibits very considerable inter-individual variability, which has led to the development of mixed effect regression techniques [26,27]. These models take account of two levels of variability: inter-individual variability and intra-individual or residual variability (as is seen in the classical regression technique). The number of parameters is therefore increased as each parameter consists of a fixed component (mean parameter) and a random component, hence the name ''mixed effect''. Tham et al. [26] proposed an empirical model to describe the effect of a combination of two drugs on tumor size in patients suffering from lung cancer. Wang et al. [27] went further by developing a similar model from a lung cancer database created from different clinical studies and therefore involving different treatments. The authors showed that some variables directly derived from model predictions (initial ''baseline'' tumor size and reduction in tumor size 3 weeks after starting treatment) were predictive indicators for survival.

If the purpose of modeling is to assess the future progression of a disease in a given patient, statistical approaches are not necessarily the most appropriate. These provide an ''average'' response provided that a sufficient database exists containing a large number of similar cases to the case in question. These models can also be made more complex by combining molecular marker activity with this simple tumor growth method to establish a multi-scale model [28].

Even so, in order to obtain a prognosis for a given tumor in a given patient, statistical modeling contains a large margin of error and does not appear appropriate. The statistical approaches may however be useful in validating and selecting the model and measuring its accuracy and robustness.

Determinist models

As described above, most of the mathematical models used clinically are based on a group of ordinal differential equations (ODE) and describe the change in tumor volume [8]. The spatial dimension (e.g. shape or site of the tumor) is not taken into account, which limits the use of the data obtained from imaging and therefore the ability to estimate the parameters in the equations. In order to compensate for this, a recent model has been developed based on morphological study of different lesions with sufficiently well defined outlines to extract the images seen after segmentation and repositioning (Fig. 1) [29]. Ordinal differential equation (ODE) and partial derived equation (PDE) models were then used, incorporating different pre-determined parameters whose values, however, were unknown. These parameters were estimated using two approaches, a population approach allowing inter-patient variability to be incorporated and an individual approach based on 2D or 3D information in order to incorporate different information such as treatment strategy.

From this work and in order to propose a simplified model which could be used in reality with the limited tumor or patient information generally available, the cell cycle was contracted into a PDE no longer structured by age, and treating a population of proliferating cells (of concentration P) (Fig. 2). Growth rate is determined by local oxygen concentration, which is given by a reaction-diffusion equation. If the oxygen concentration is too low (hypoxia), not only do the cells not proliferate but they move into the quiescent phase (shown as Q) (the phase in which the tumor cells remains alive but cells do not proliferate). Conversely, if the oxygen concentration increases, the cells can return to the proliferative phase. The proliferative/quiescent cell ratio is an indicator of tumor aggression. Cell proliferation leads to an increase in volume, which is described as the divergence of a velocity field, which has to be determined. This velocity field has nothing to do with the velocity, for example, of infiltrating cells, but describes the overall movement of the tissue due to its increase in volume limited by the pressure of the surrounding environment according to Darcy's law, with permeability depending on the tissue (healthy or tumor) [30]. Finally, oxygen concentration is given by a diffusion equation which depends on the type of tissue and which reflects vascularization with absorption factors due to consumption by tumor cells.

In summary, the equations which describe changes in density P and Q are shown below:

$$\frac{\partial P}{\partial t} + \nabla \cdot (\boldsymbol{v} P) = (2\gamma - 1)P + \gamma Q,$$

$$\frac{\partial Q}{\partial t} + \nabla \cdot (\boldsymbol{v} Q) = (1 - \gamma)P + \gamma Q$$

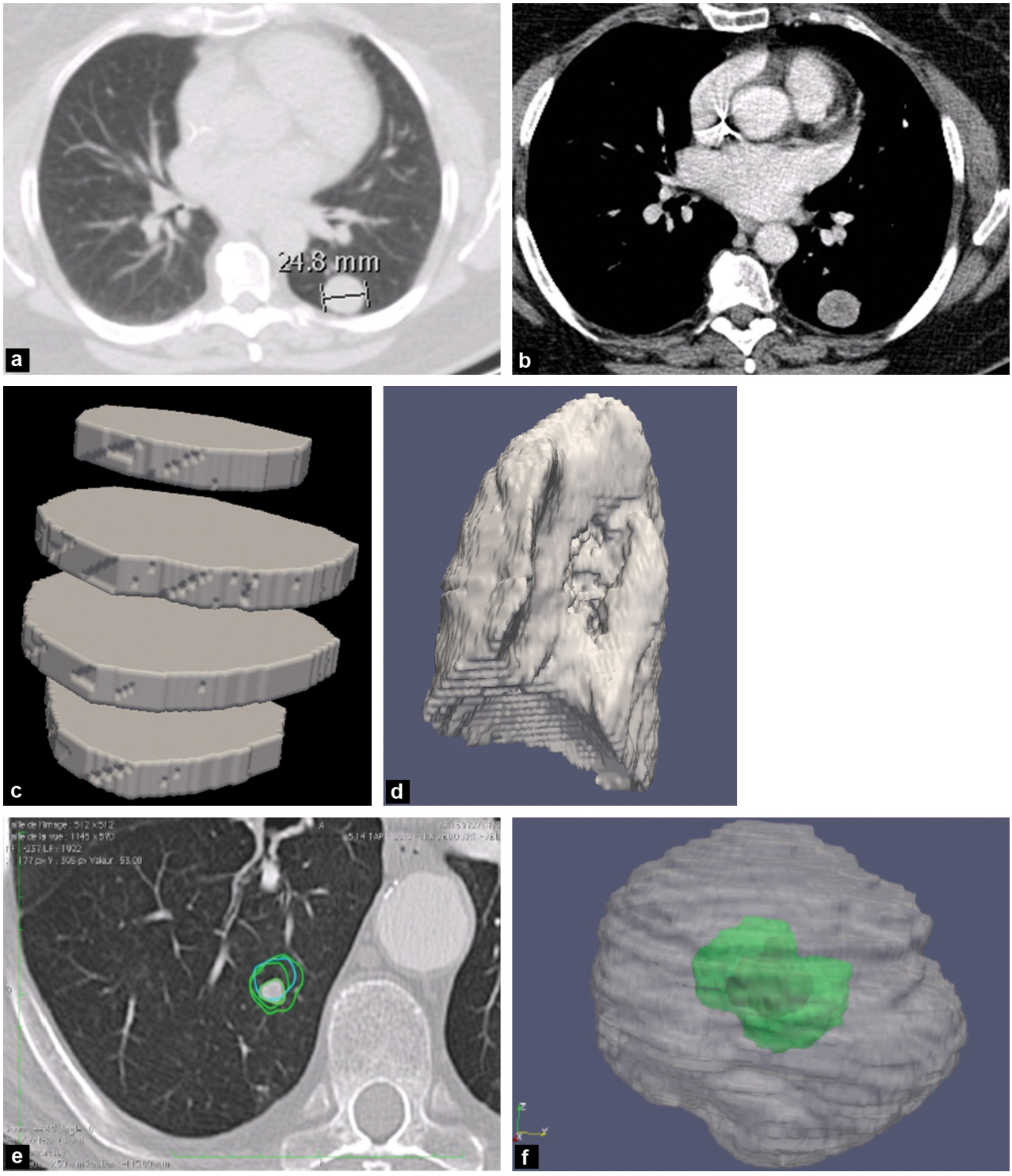


Figure 1. Segmentation and repositioning of images. a, b: axial computed tomography sections showing a left lower lobe lung nodule in the pulmonary and mediastinal windows respectively; c: the nodule is segmented in sections and visualized in 3D; d: the lung volume is also segmented; e: several contours are shown illustrating the change over a same volume section, the shape and precision of a lung nodule on the subsequent CT scans after repositioning; f: segmentation, repositioning and 3D visualization of the same nodule on three successive investigations.

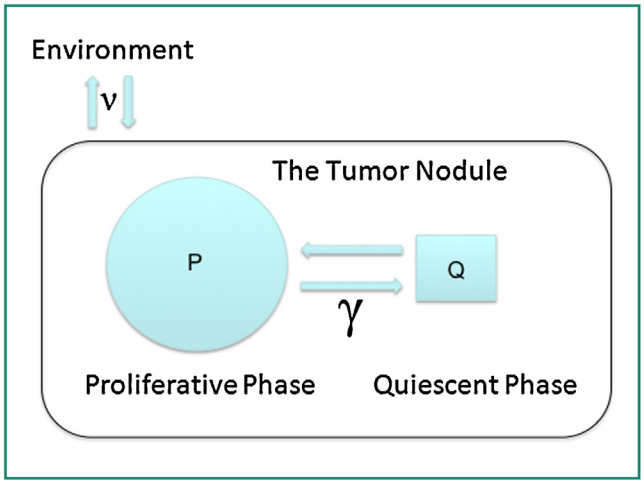


Figure 2. Basic principle of modeling tumor growth. The proliferating phase, *P*, and the quiescent phase, *Q*, depend on the concentration of nutrients and oxygen (linked to γ) provided in a simplified way by vascularization.

where the function γ describes the presence or absence of sufficient nutrients:

$$\gamma = \frac{1 + \tanh(C - C_{hyp})}{2}$$

where *C* represents local oxygen concentration. The hypoxia threshold C_{hyp} is a model parameter, which describes the sensitivity of cells to hypoxia. As seen previously, in this case cell movement is deemed to be due only to cell division and the velocity **v** in the system follows Darcy's law.

Although this model is greatly simplified, it already contains several parameters, which need to be identified whereas the only finding provided by imaging is tumor volume, which is the sum of variables $P + Q$ in the model. Based only on morphological imaging, i.e. by studying volume, the site, shape and uptake of a tumor and any growth, information obtained from imaging examinations is therefore very limited.

The calculation strategy is as follows: for a given patient, the images must first be processed digitally (Fig. 1) and then in order to use the PDE model shown schematically in Fig. 2, its parameters must be determined. This is achieved by solving an inverse problem involving a large number of calculations using several radiological investigations as the input data. Under favorable conditions a personalized prediction can then be obtained.

These models are undergoing preclinical evaluation for gliomas, lung metastases (Fig. 3) and some stromal tumors (gastrointestinal stromal tumor [GIST]) (Fig. 4). These tumors have the advantage that it is easy to define their outlines and can be followed up for relatively long periods of time with or without treatment. A large amount of information about their progression is therefore available. As shown in Fig. 3, it is already possible to obtain a quantitative prediction for untreated lung metastases. A prediction is not yet possible for hepatic GIST metastases (Fig. 4), although the response to treatment and loss of treatment response phase can be reproduced. The modeling techniques are described in detail in reference [30].

Future prospects

Although the clinical use of spatial mathematical models is far from being actually effective, they have many short and medium term future prospects in the clinical assessment in surgery or interventional radiology by determining tumor margins or optimizing needle positioning (for example, thermal heat ablation or cryotherapy).

Whilst some aspects of tumor growth are not determinist (for example, spontaneous genetic mutations and the emergence of phenotypes which are resistant to therapy) and cannot therefore be incorporated into these models for a specific approach to a given patient, this work can enable early changes due to these mutations to be identified from a deviation from the medical findings in relation to the digital prediction. Treatments can therefore be adjusted earlier.

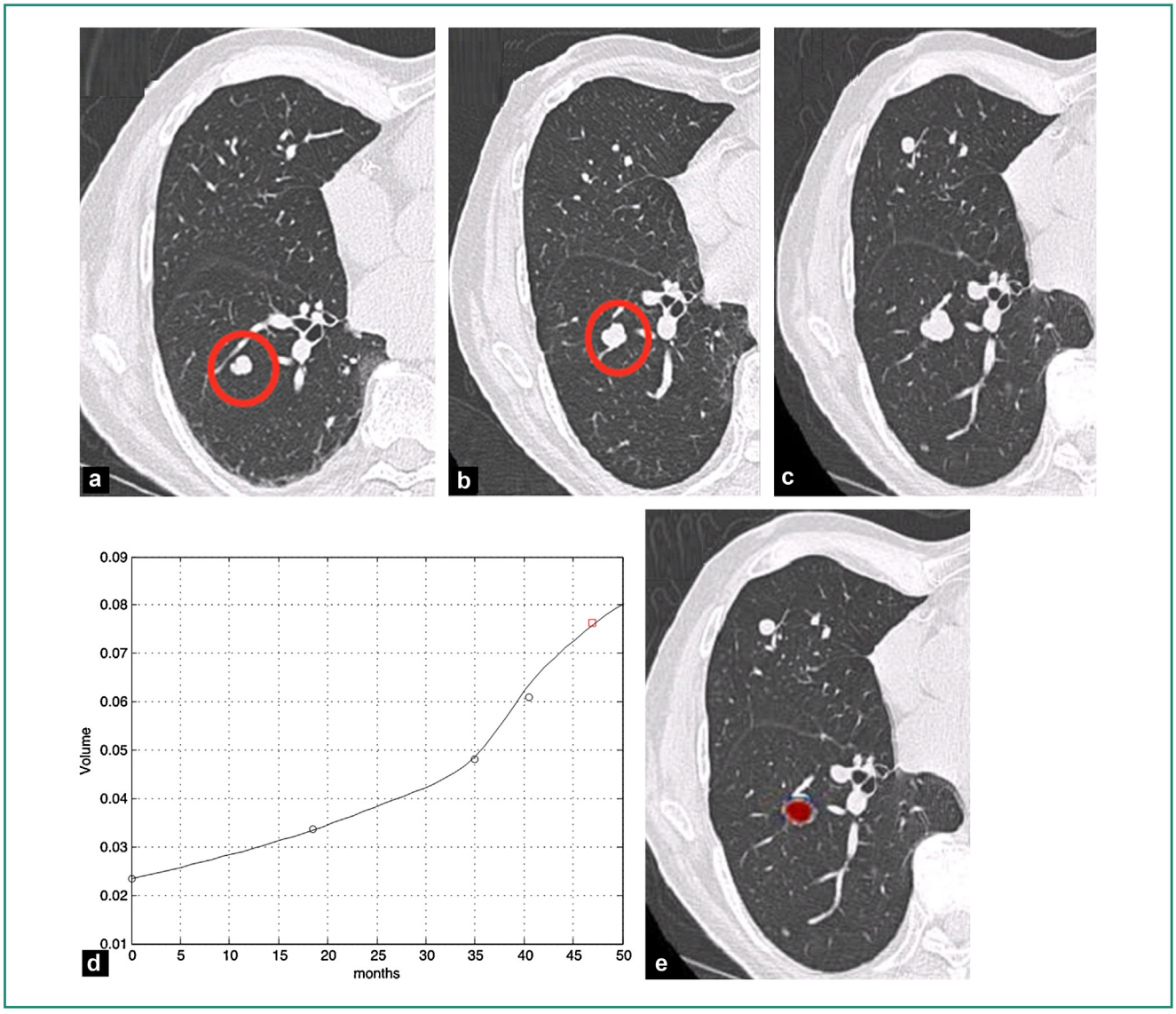


Figure 3. Modeling tumor growth of lung metastases. a, b, c: axial computed tomography sections showing a right lower lobe lung nodule on successive CT scans without any treatment. Only images a and b are used in the calculation. Subsequent investigations are simply used to validate our method; d: change in volume of the nodule over time: actual observations (round) and those obtained from calibrated modeling (curve). The red square is the volume actually measured on an investigation performed after the model was calibrated; e: computed tomography axial section with representation of the tumor calculated at the same time (red) as investigation of the image c.

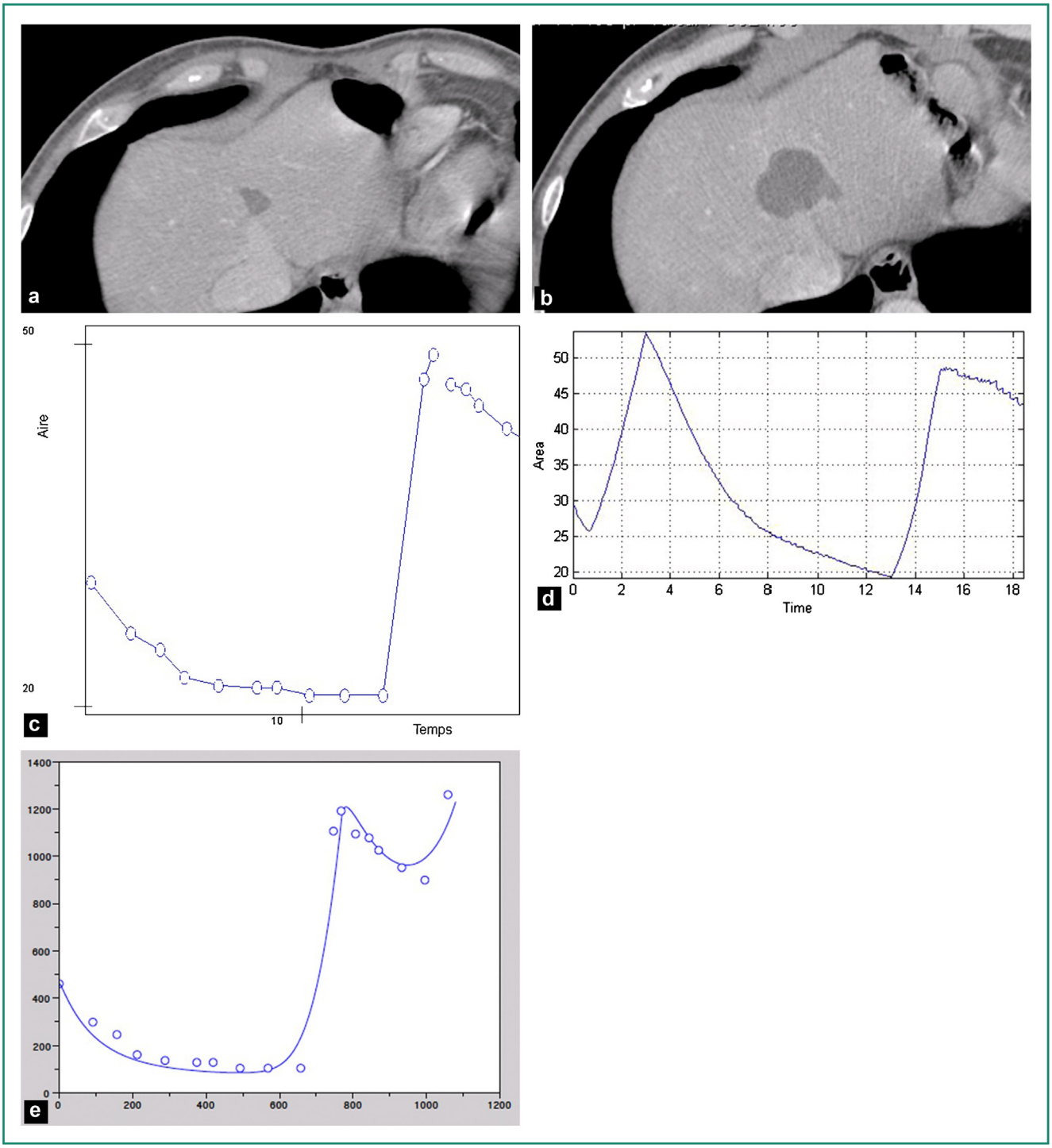


Figure 4. Modeling of tumor growth of hepatic GIST metastases. a, b: computed tomography axial sections with injection showing a hepatic nodule in segment IV on two successive scans; c: change in volume over time on the actual observations. These changes take account of successive anti-tyrosine kinase treatments (decreased phase) followed by an anti-angiogenic after failure to respond further to treatment; d: change in volume of the nodule over time from modeling. This initial completely spatial model (PDE) takes, at least qualitatively, account of the control phase with the anti-tyrosine kinase then the loss of response and finally the control by anti-angiogenic. These results are not predictions as all of the data are used to obtain the simulated curves; e: this second modeling (ODE) takes quantitative account in terms of the cell population in the control phase and then the loss of response. These results are not predictions as all of the data are used to obtain the simulated curves.

Conclusion

Whereas many technical challenges remain to be resolved and cannot be ignored, mathematical modeling of tumor growth even if simplistic is now a reality. Imaging appears to be a valuable aid in solving the different problems raised. The input of further information from functional imaging will help to facilitate the resolution of current models and either to predict the development and use of the more precise models in order to come closer to the real life biological situation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Krajewski KM, Guo M, Van den Abbeele AD, Yap J, Ramaiya N, Jagannathan J, et al. Comparison of four early posttherapy imaging changes (EPTIC; RECIST 1.0, tumor shrinkage, computed tomography tumor density, Choi criteria) in assessing outcome to vascular endothelial growth factor-targeted therapy in patients with advanced renal cell carcinoma. Eur Urol 2011;59:856—62.

[2] Li SP, Padhani AR. Tumor response assessments with diffusion and perfusion MRI. J Magn Reson Imaging 2012;35:745—63.

[3] Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer 2004;4:891—9.

[4] Desar IM, ter Voert EG, Hambrock T, van Asten JJ, van Spronsen DJ, Mulders PF, et al. techniques demonstrate early vascular changes in renal cell cancer patients treated with sunitinib: a pilot study. Cancer Imaging 2011;11:259—65.

[5] Anderson AR, Chaplain MA. Continuous and discrete mathematical models of tumor-induced angiogenesis. Bull Math Biol 1998;60:857—99.

[6] Gatenby RA, Gawlinski ET. A reaction-diffusion model of cancer invasion. Cancer Res 1996;56:5745—53.

[7] Sherratt JA, Chaplain MA. A new mathematical model for avascular tumor growth. J Math Biol 2001;43:291—312.

[8] Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, et al. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res 2004;64:1094—101.

[9] Modok S, Scott R, Alderden RA, Hall MD, Mellor HR, Bohic S, et al. Transport kinetics of four- and six-coordinate platinum compounds in the multicell layer tumor model. Br J Cancer 2007;97:194—200.

[10] Byrne H, Drasdo D. Individual-based and continuum models of growing cell populations: a comparison. J Math Biol 2009;58:657—87.

[11] Drasdo D, Hohme S. A single-cell-based model of tumor growth in vitro: monolayers and spheroids. Phys Biol 2005;2:133—47.

[12] Alarcon T, Byrne HM, Maini PK. A cellular automaton model for tumor growth in inhomogeneous environment. J Theor Biol 2003;225:257—74.

[13] Mansury Y, Kimura M, Lobo J, Deisboeck TS. Emerging patterns in tumor systems: simulating the dynamics of multicellular clusters with an agent-based spatial agglomeration model. J Theor Biol 2002;219:343—70.

[14] Ramis-Conde I, Drasdo D, Anderson AR, Chaplain MA. Modeling the influence of the E-cadherin-beta-catenin pathway in cancer cell invasion: a multiscale approach. Biophys J 2008;95:155—65.

[15] Macklin P, McDougall S, Anderson AR, Chaplain MA, Cristini V, Lowengrub J. Multiscale modeling and nonlinear simulation of vascular tumor growth. J Math Biol 2009;58:765—98.

[16] Gerisch A, Chaplain MA. Mathematical modeling of cancer cell invasion of tissue: local and non-local models and the effect of adhesion. J Theor Biol 2008;250:684—704.

[17] Hillen T, Painter KJ. A user's guide to PDE models for chemotaxis. J Math Biol 2009;58:183—217.

[18] Preziosi L, Ambrosi D, Verdier C. An elasto-visco-plastic model of cell aggregates. J Theor Biol 2010;262:35—47.

[19] Ambrosi D, Duperray A, Peschetola V, Verdier C. Traction patterns of tumor cells. J Math Biol 2009;58:163—81.

[20] Bekkal Brikci F, Clairambault J, Ribba B, Perthame B. An age-and-cyclin-structured cell population model for healthy and tumoral tissues. J Math Biol 2008;57:91—110.

[21] Clairambault J. A step toward optimization of cancer therapeutics. Physiologically based modeling of circadian control on cell proliferation. IEEE Eng Med Biol Mag 2008;27:20—4.

[22] Levi F, Karaboue A, Gorden L, Innominato PF, Saffroy R, Giacchetti S, et al. Cetuximab and circadian chronomodulated chemotherapy as salvage treatment for metastatic colorectal cancer (mCRC): safety, efficacy and improved secondary surgical resectability. Cancer Chemother Pharmacol 2011;67:339—48.

[23] Ribba B, Colin T, Schnell S. A multiscale mathematical model of cancer, and its use in analyzing irradiation therapies. Theor Biol Med Model 2006;3:7.

[24] Ribba B, Saut O, Colin T, Bresch D, Grenier E, Boissel JP. A multiscale mathematical model of avascular tumor growth to investigate the therapeutic benefit of anti-invasive agents. J Theor Biol 2006;243:532—41.

[25] Billy F, Ribba B, Saut O, Morre-Trouilhet H, Colin T, Bresch D, et al. A pharmacologically based multiscale mathematical model of angiogenesis and its use in investigating the efficacy of a new cancer treatment strategy. J Theor Biol 2009;260:545—62.

[26] Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, et al. A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. Clin Cancer Res 2008;14:4213—8.

[27] Wang Z, Zhang L, Sagotsky J, Deisboeck TS. Simulating non-small cell lung cancer with a multiscale agent-based model. Theor Biol Med Model 2007;4:50.

[28] Bueno L, de Alwis DP, Pitou C, Yingling J, Lahn M, Glatt S, et al. Semi-mechanistic modeling of the tumor growth inhibitory effects of LY2157299, a new type I receptor TGF-beta kinase antagonist, in mice. Eur J Cancer 2008;44:142—50.

[29] Konukoglu E, Clatz O, Menze BH, Stieltjes B, Weber MA, Mandonnet E, et al. Image guided personalization of reaction-diffusion type tumor growth models using modified anisotropic eikonal equations. IEEE Trans Med Imaging 2010;29:77—95.

[30] Ambrosi D, Preziosi L. Cell adhesion mechanisms and stress relaxation in the mechanics of tumors. Biomech Model Mechanobiol 2009;8:397—413.