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Variable order 3D models of bone remodelling

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Abstract. This paper presents simulations of a three-dimensional model of the bone remodelling process. The model consists of a set of variable order partial differential equations, in which the varying order depends on the presence of tumour cells. The simulations are of a two-dimensional bone, to make visualisation simpler. They show that this model corresponds to the known evolution of bone remodelling, and is simpler than integer order models found in the literature.

Key words: variable order derivatives, bone remodelling, cancer.

1. Introduction

Bone tissue, just like every other tissue in the human body, undergoes constant remodelling: it is absorbed by cells termed osteoclasts and rebuilt by cells termed osteoblasts. It is possible to model this remodelling activity using a system of differential equations, as in [7]. Such a model shows how bone remodelling may lead to periodic oscillations of the bone mass, around a steady state value. This model can be adapted to include the effects of a tumour, which modifies the equilibrium of bone remodelling for its own profit. It is also possible to extend the model, accounting for diffusion processes. This leads to a system of partial differential equations. These improvements of the model have been done in [1].

Diffusion processes in biological systems are often anomalous [9]; this can be modelled using fractional derivatives [5]. And the model adaptation to the tumourous case can be simplified by considering that the fractional derivative is of variable order: the effects of the tumour correspond to the case of subdiffusion [12]. Thus, variable order systems of partial differential equations can be used to model bone remodelling, of both healthy and tumourous bone tissue, more concisely and easily than using integer order derivatives only.

The effects of diffusion have always been considered in the literature as taking place in one dimension (1D) only, as if the bone were a straight line, or, in other words, as if the bone had a neglectable section, when compared to its length. In this paper, models are presented for the first time in three dimensions (3D); for ease of visualisation, simulations are presented in two dimensions (2D): the bone is now approximated by a rectangle, with neglectable thickness. Equations are solved using a mixed method. The extension of this numerical method to 3D is straightforward.

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Section 2 presents the original, integer order models, from [1, 7]. Section 3 presents the variable order model from [12], extended to 3D. Simulation results when one of the dimensions is neglectable are found in Section 4. Section 5 discusses these results and offers a short conclusion.

2. The original integer order models

The model for healthy bone tissue remodelling of [7] has the form of an S-system [14]. The normalised number of osteoclasts $C(t)$ and the normalised number of osteoblasts $B(t)$ are related through biochemical autocrine factors g_{CC} and g_{BB}, and also through paracrine factors g_{BC} g_{CB}. The density of the bone $\mathfrak{z}(t)$ is determined by the extent to which $C(t)$ and $B(t)$ exceed their steady state levels C_{SS} and B_{SS}. Below these steady state levels, the populations of osteoclasts and osteoblasts are assumed to consist of less differentiated cells that are unable to resorb or build bone, but are able to participate in autocrine and paracrine signaling. Constants κ_C and κ_B represent bone resorption and formation activity.

$$\frac{\mathrm{d}C(t)}{\mathrm{d}t} = \alpha_C C(t)^{g_{CC}} B(t)^{g_{BC}} - \beta_C C(t), \tag{1}$$

$$\frac{\mathrm{d}B(t)}{\mathrm{d}t} = \alpha_B C(t)^{g_{CB}} B(t)^{g_{BB}} - \beta_B B(t), \tag{2}$$

$$\frac{\mathrm{d}\mathfrak{z}(t)}{\mathrm{d}t} = -\kappa_C \max\left[0, C(t) - C_{ss}\right] + \kappa_B \max\left[0, B(t) - B_{ss}\right]. \tag{3}$$

The 1D model for bone with an osteolytic tumour in [1] has the autocrine and paracrine factors altered by the tumours through r_{ij} parameters. The tumour density $T(x,t)$ has a Gompertz form of constant growth $\gamma_T > 0$, independent of bone loss, corresponding to a possible maximum tumour size of L_T, as seen in Fig. 1. The diffusion coefficients are σ_C, σ_B and σ_T; as to $\sigma_{\mathfrak{z}}$, it does not represent diffusion of (healthy) bone cells, but is rather

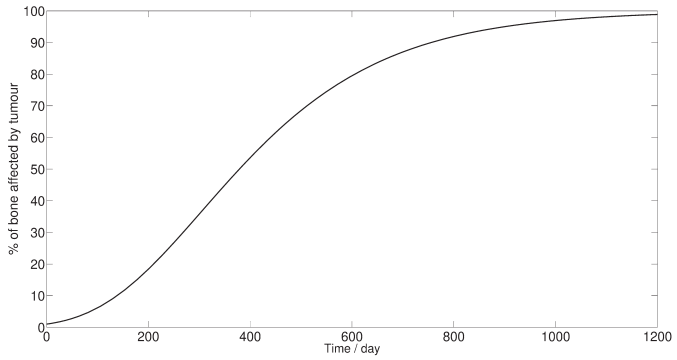

Fig. 1. Tumour evolution

intended to model the stochastic nature of bone remodelling.

$$\frac{\partial C(x,t)}{\partial t} = \sigma_C \frac{\partial^2 C(x,t)}{\partial x^2} + \alpha_C C(x,t)^{\left(g_{CC}\left(1+r_{CC}\frac{T(t)}{L_T}\right)\right)} B(x,t)^{\left(g_{BC}\left(1+r_{BC}\frac{T(x,t)}{L_T}\right)\right)} - \beta_C C(x,t), \tag{4}$$

$$\frac{\partial B(x,t)}{\partial t} = \sigma_B \frac{\partial^2 B(x,t)}{\partial x^2} + \alpha_B C(x,t)^{\left(\frac{g_{CB}}{1+r_{CB}\frac{T(x,t)}{L_T}}\right)} B(x,t)^{\left(g_{BB}-r_{BB}\frac{T(x,t)}{L_T}\right)} - \beta_B B(x,t), \tag{5}$$

$$\frac{\partial T(x,t)}{\partial t} = \sigma_T \frac{\partial^2 T(x,t)}{\partial x^2} + \gamma_T T(t) \log \frac{L_T}{T(x,t)}, \tag{6}$$

$$\frac{\partial \mathfrak{z}(x,t)}{\partial t} = \sigma_{\mathfrak{z}} \frac{\partial^2 \mathfrak{z}(x,t)}{\partial x^2} - \kappa_C \max\left[0, C(x,t) - C_{ss}\right] + \kappa_B \max\left[0, B(x,t) - B_{ss}\right]. \tag{7}$$

3. The variable order model

Variable order derivatives generalise the concept of fractional (or, more exactly, non-integer) order derivatives, which are themselves a generalisation of the usual concept of integer order derivatives (and integrals, which are derivatives of negative order). Let us denote the derivative of order n as D^n; then by definition

$$D^1 f(t) = \lim_{h\to 0} \frac{f(t) - f(t-h)}{h} \tag{8}$$

and by mathematical induction we get

$$D^n f(t) = \lim_{h\to 0} \frac{\sum_{k=0}^{n} (-1)^k \binom{n}{k} f(t-kh)}{h^n}. \tag{9}$$

This can be generalised for an arbitrary order $\alpha \in \mathbb{R}$ as

$${}_cD_t^\alpha f(t) = \lim_{h\to 0^+} \frac{\sum_{k=0}^{\lfloor \frac{t-c}{h} \rfloor} (-1)^k \binom{\alpha}{k} f(t-kh)}{h^\alpha}, \tag{10}$$

$$\binom{a}{b} = \begin{cases} \frac{\Gamma(a+1)}{\Gamma(b+1)\Gamma(a-b+1)}, \text{ if } a,b,a-b \in \mathbb{R}\backslash\mathbb{Z}^-, \\ \frac{(-1)^b \Gamma(b-a)}{\Gamma(b+1)\Gamma(-a)}, \text{ if } a \in \mathbb{Z}^- \wedge b \in \mathbb{Z}_0^+, \\ 0, \text{ if } \left((b \in \mathbb{Z}^- \vee b-a \in \mathbb{N}) \wedge a \in \mathbb{R}\backslash\mathbb{Z}^-\right) \\ \qquad \vee (a,b \in \mathbb{Z}^- \wedge |a| > |b|). \end{cases} \tag{11}$$

This definition (one among other possible ones) is due to the work of Grünwald and Letnikoff [11, 13, 18, 19], and uses the Γ function to generalise combinations. Notice that terminals c and t, similar to those of integrals, appear for all real non-integer orders.

As the order α is real, it can change continuously with time (the order of an integer derivative can only change in steps); one of the possible ways of taking this variation of the order into account is the recursive definition $\mathscr{D}$ of papers [8, 10, 15], used in what follows for the variable order derivative ${}_0^{\mathscr{D}}\mathrm{D}_t^{\alpha(t)}$, and approximated with a finite sample time $h = 1$ day as follows:

$${}_0^{\mathscr{D}}\mathrm{D}_t^{\alpha(t)} f(t) \approx \left(\frac{f(t)}{h^{\alpha(t)}} - \sum_{r=1}^{n} (-1)^r \binom{-\alpha(t)}{r} {}_0^{\mathscr{D}}\mathrm{D}_{t-rh}^{\alpha(t)} f(t) \right). \tag{12}$$

In the model presented in [12] it is the variable order $\alpha(t,x,y,z)$ that induces the response of the tumourous bone. The order is related to the tumour through (17), and changes as well with time, with a constant θ scale factor. Its 3D version will now be

$$\frac{\partial^\alpha C}{\partial t^\alpha} = \sigma_C \frac{\partial^2 C}{\partial x^2} + \sigma_C \frac{\partial^2 C}{\partial y^2} + \sigma_C \frac{\partial^2 C}{\partial z^2} + \alpha_C C(t)^{g_{CC}} B^{g_{BC}} - \beta_C C, \tag{13}$$

$$\frac{\partial^\alpha B}{\partial t^\alpha} = \sigma_B \frac{\partial^2 B}{\partial x^2} + \sigma_B \frac{\partial^2 B}{\partial y^2} + \sigma_B \frac{\partial^2 B}{\partial z^2} + \alpha_B C(t)^{g_{CB}} B(t)^{g_{BB}} - \beta_B B(t), \tag{14}$$

$$\frac{\partial T}{\partial t} = \sigma_T \frac{\partial^2 T}{\partial x^2} + \sigma_T \frac{\partial^2 T}{\partial y^2} + \sigma_T \frac{\partial^2 T}{\partial z^2} + \gamma_C T \log \frac{L_T}{T}, \tag{15}$$

$$\frac{\partial \mathfrak{z}}{\partial t} = \sigma_{\mathfrak{z}} \frac{\partial^2 \mathfrak{z}}{\partial x^2} + \sigma_{\mathfrak{z}} \frac{\partial^2 \mathfrak{z}}{\partial y^2} + \sigma_{\mathfrak{z}} \frac{\partial^2 \mathfrak{z}}{\partial z^2} - \kappa_C \left[0, C - C_{ss}\right] + \kappa_B \left[0, B - B_{ss}\right], \tag{16}$$

$$\alpha = 1 - T\theta t. \tag{17}$$

In these equations, the dependence of $\alpha(t,x,y,z)$, $C(t,x,y,z)$, $B(t,x,y,z)$, $T(t,x,y,z)$ and $\mathfrak{z}(t,x,y,z)$ on space and time has been dropped to alleviate the notation. Notice that, in both the original and the variable order model, T is limited to the $[0,1]$ range, by definition.

The new model's steady-state is the same as that of the model for healthy bone, and most parameters remain with the same value, while the associated activity of osteoclasts and osteoblasts in bone mass must differ from the original case. Then, a new bone resorption-formation ratio, $R = \frac{\int_0^{\bar{t}} \max[0, C(t) - C_{ss}]}{\int_0^{\bar{t}} \max[0, B(t) - B_{ss}]}$, is determined between 0 and $\bar{t}$, that corresponds to the completion time of a single cycle of $C(t)$ and $B(t)$ in the new model. This method is the same followed in [1], for a healthy bone environment. Bone resorption and formation activities are then recalculated and given by $\kappa_C = rR$ and $\kappa_B = r$.

4. Simulation results

Simulation parameters are given in Table 1. The initial number of osteoblasts is constant and taken from [1]; the initial (non-constant) distribution of osteoclasts is also based upon that used in [1] (in 1D), and is given in the figures below. Simulations were carried out using Simulink. Partial differential equations were solved using, for time derivatives, a fixed-step third-order method provided by the software, and, for space derivatives, a fixed-step centred finite difference method, for which the bone was approximated as a 10×10 square.

Figure 2 shows the results of a simulation in which there is no tumour ($T(x,t,z,t) = 0$ always and everywhere). Figures 3 and 4 show a simulation in which a tumour begins in one point and spreads. The simulation time is 700 days (slightly under 2 years) in both cases. Notice that healthy bone has a mass that oscillates around 100%, both in space and in time, with a period under one year. Equation parameters are adjusted so that this behaviour takes place, as it is what can be observed *in vivo*. The growth of the tumour causes a steady decrease of bone mass, even in zones not yet affected by the tumour itself, which is a consequence of the deregulation of the biochemi-

Table 1
Variables and parameters used in simulations, from [12]. Parameters, in both meaning and value, follow what was presented in [1]. In the case of the model of section 3, units day^{-1} are replaced by pseudo-units day$^{-\alpha(t,x,y,z)}$

Variables	Description		Units
t	Time		days
x, y, z	Spatial dimensions		non-dimensional
C	Number of osteoclasts		–
B	Number of osteoblasts		–
z	Bone mass		%
T	Bone metastases size		%
Parameters	Description		Units
α_C	Osteoclasts activation rate	3	day^{-1}
α_B	Osteoblasts activation rate	4	day^{-1}
β_C	Osteoclasts apoptosis rate	0.2	day^{-1}
β_B	Osteoblasts apoptosis rate	0.02	day^{-1}
g_{CC}	Osteoclasts autocrine regulator	1.1	–
g_{BC}	Osteoclasts paracrine regulator	-0.5	–
g_{CB}	Osteoblasts paracrine regulator	1.0	–
g_{BB}	Osteoblasts autocrine regulator	0	–
L_T	Maximum size of bone metastases	100	%
$B(0)$	Initial number of osteoblasts	316	–
$z(0)$	Initial bone mass percentage	100	%
$T(0)$	Initial bone mass percentage	1	%
$\alpha(t)$	Time dependent variable order	–	–
θ	Variable order gradient	8.33×10^{-9}	–
κ_C	Bone resorption rate (for healthy bone)	0.45	% day^{-1}
κ_B	Bone formation rate (for healthy bone)	0.0048	% day^{-1}
κ_C	Bone resorption rate (for tumourous bone)	0.1548	% day^{-1}
κ_B	Bone formation rate (for tumourous bone)	6.8176×10^{-4}	% day^{-1}
γ_T	Bone metastases growth rate	0.004	% day^{-1}
σ_C	Diffusion coefficient of osteoclasts	1×10^{-6}	day^{-1}
σ_B	Diffusion coefficient of osteoblasts	1×10^{-6}	day^{-1}
σ_T	Diffusion coefficient of tumour cells	1×10^{-6}	day^{-1}
σ_3	Diffusion coefficient of bone cells	1×10^{-6}	day^{-1}

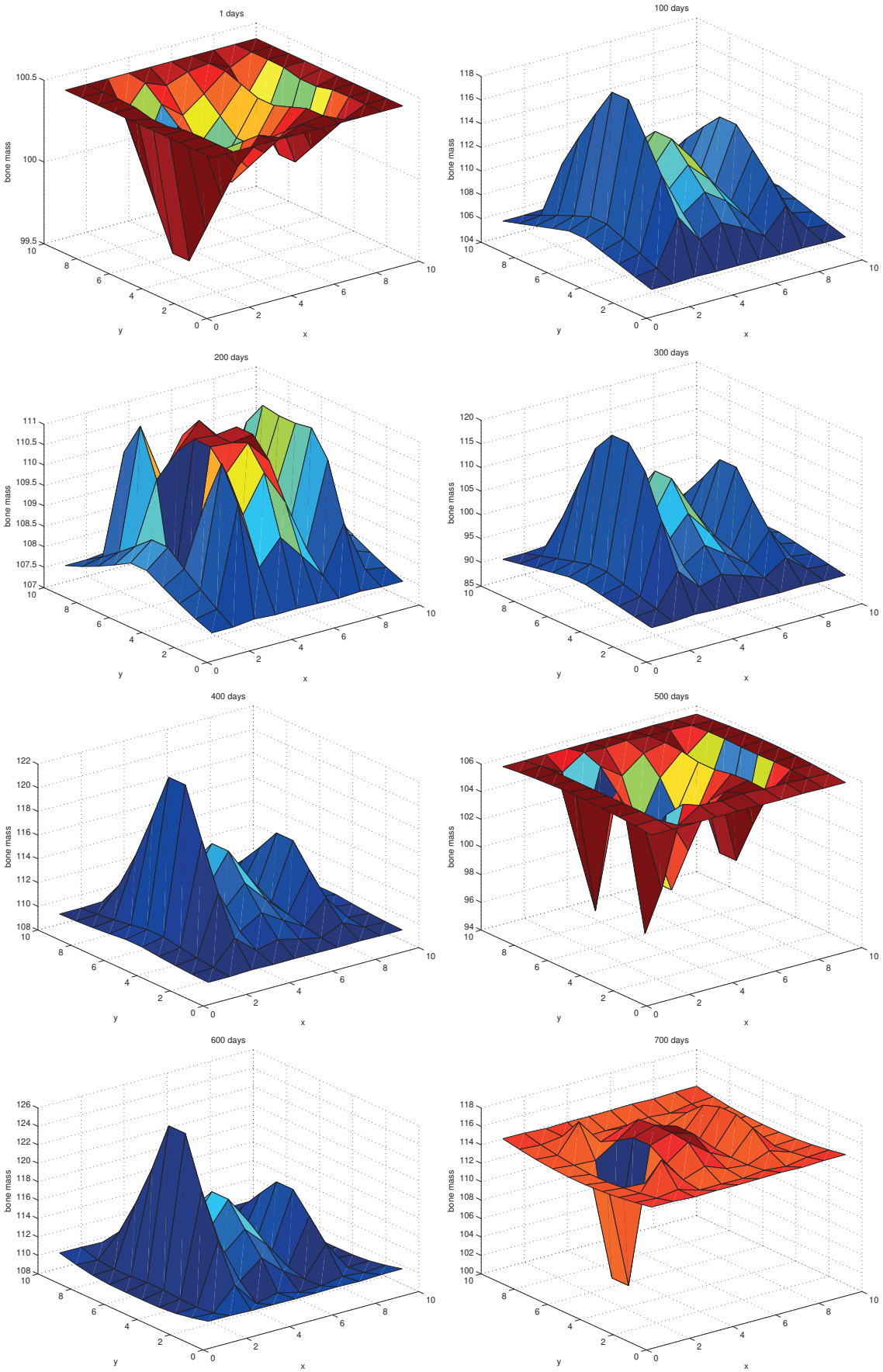

Fig. 2. Bone mass evolution for healthy bone

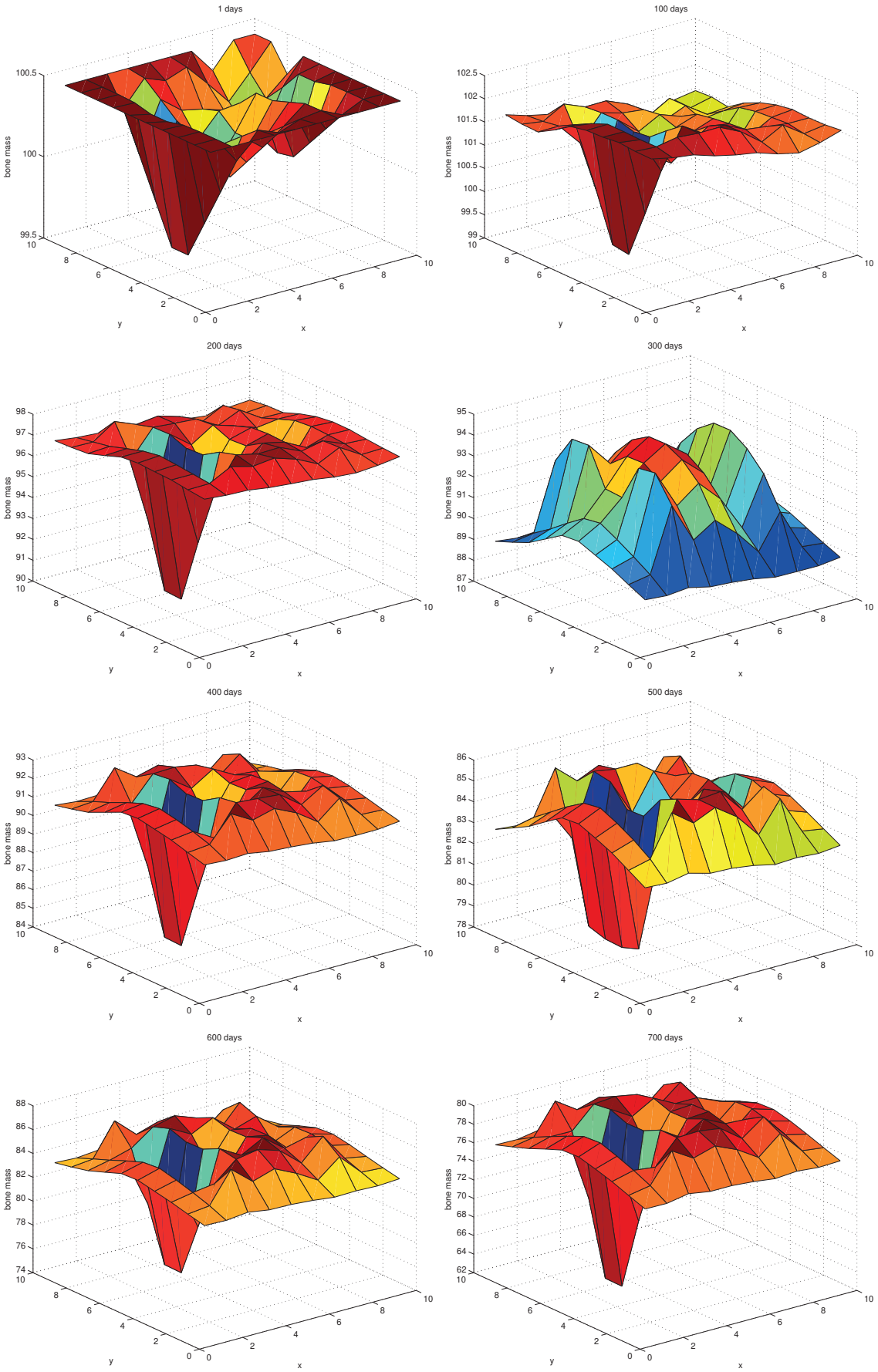

Fig. 3. Bone mass evolution in the presence of a tumour

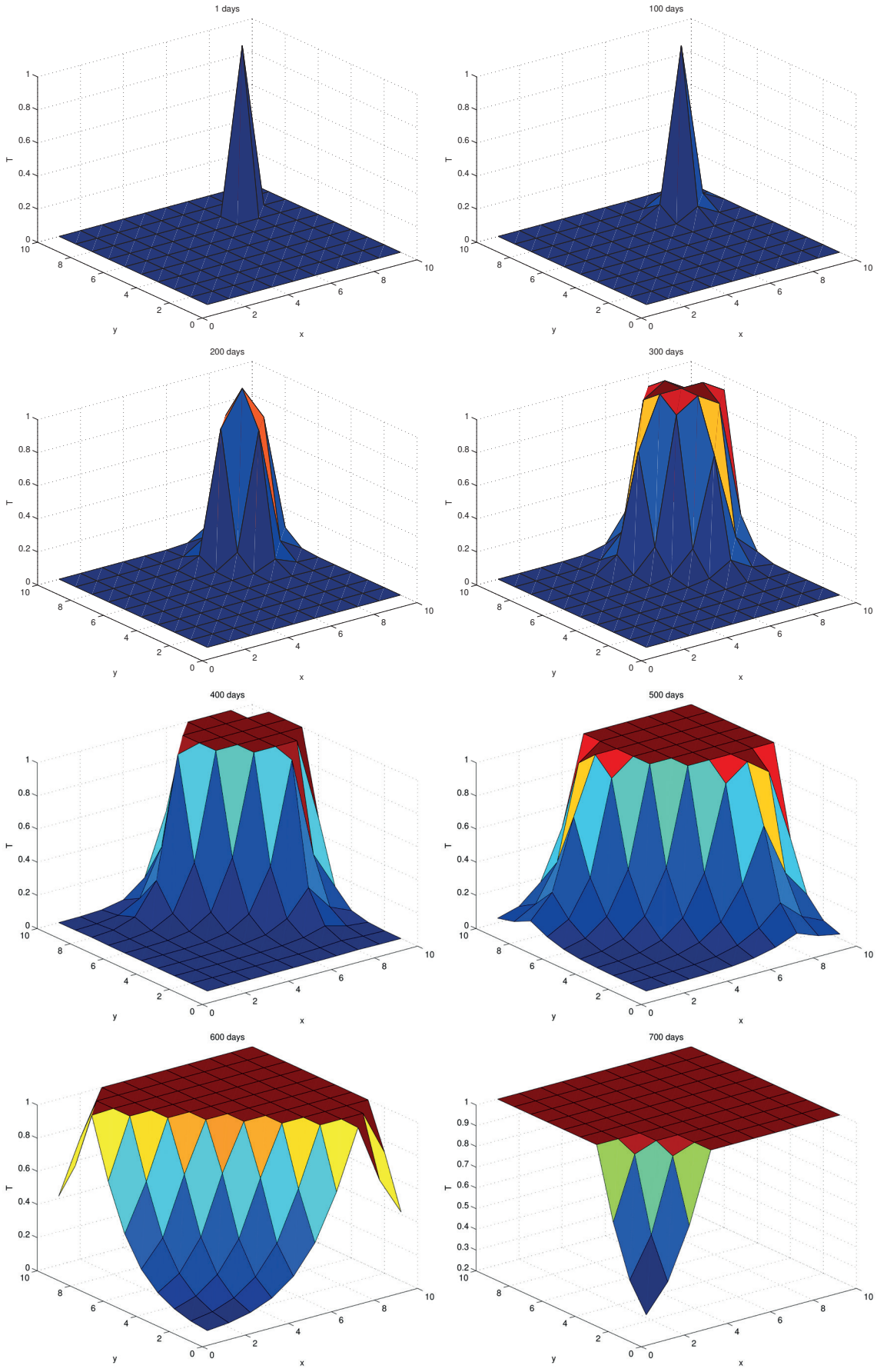

Fig. 4. Tumour evolution in the case shown in Fig. 3

cal equilibria, and of the diffusion of osteoblasts and osteoclasts. This behaviour corresponds to a particular type of bone lesion called osteolytic disease, in which mass decreases in this wise. Other bone cancers are osteoblastic, and in that situation bone regulation is disrupted so that its mass increases undesirably; this could be simulated with a different variation of the order of the fractional derivatives.

5. Discussion and conclusions

Models for bone remodelling based upon the corresponding biochemical processes can give important insights about how bone tissue behaves, and can support the development of clinical decision systems for bone pathologies, and for efficient targeted therapies. Thus simplified models mimicking bone behaviour with tumours are important for a treatment tailored for each particular patient. This paper presents one further step in new approaches to the existing biochemical models [1,7], by including diffusion in more than one dimension. The use of variable order derivatives [12] allows a reduced set of parameters to describe results similar to those from the original formulations, and a more compact model is achieved, with good qualitative simulations of what is known for the bone dynamics. These are the strengths of this variable order model over integer order models: taking into account anomalous diffusion, which integer order derivatives do not, and modelling all the phenomena with less parameters.

Future work should address the following points:

- There are integer order models with a more detailed description of the biochemical processes involved [6,17]. They too could be simplified using variable order derivatives.
- Mechanical solicitations also affect bone remodelling [2,3]. The biochemical effects of these mechanical solicitations can be found and incorporated in the models, coupled with the biochemical physiology already analysed.
- It is possible to include in the models of tumours the results of cancer treatments [1,6]. Pharmacokinetic and pharmacodynamic effects can be included. Simulations for these cases are still wanting.
- Optimal control and adaptive control can be used to find the best possible treatment for a particular case, provided that accurate parameters can be found [16]. These control techniques can be employed here as well.

Concerning this last issue, it surely would be most desirable to have experimental data to find values for the coefficients of the models. It is even possible to conceive different parameters being found for particular patients, allowing treatments adjusted in advance for each case (personalised medicine). It is possible that such data may be extrapolated from experiments with animals, since collecting the data from humans is likely to be too expensive, and, furthermore, unethical, due to the invasiveness of collection procedures. Data could also result from medical imaging techniques [4]. Model parameters in this paper are little more than educated guesses by clinicians and oncobiologists at the magnitude of the values; while current results are reasonable from the qualitative point of view, finding actual experimental values is probably the model's biggest challenge.

The analysis and simulation of these models may bring new insights on bone physiology and provide a better understanding of cancer treatments, thus supporting the relief of the millions of patients diagnosed each year.

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