Tumor growth models to generate pathologies for surgical training simulators

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Abstract

Many virtual reality based surgical training simulators have been presented in the last few years. These systems promise to alleviate the lack of realistic training possibilities common to minimally invasive procedures. Virtual reality allows for riskless training on a wide range of findings in a condensed period of time. We investigated different methods for the generation of tumor models suitable for surgical training simulators. The goal of our research is a high fidelity hysteroscopy simulator which provides an individual surgical scene for every training. Emphasis was placed on the modeling of growth processes leading to the generation of macroscopically realistic findings of the most common pathologies in hysteroscopy, namely polyps and myomas found in the uterine cavity. Both a cellular automaton and a particle based tumor growth model are presented and discussed.

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1. Introduction

Endoscopic procedures have become increasingly popular in medical treatment over the past decades, mainly as they reduce the time of recovery for the patients and the size of the visible incisions (Schwenk et al., 1998). There is consensus that this type of interventions requires extensive training which nowadays can only be provided rudimentarily and is largely limited to a few assisted interventions. In the last few years, many surgical training simulators have been presented that promise to overcome the limitations of current training paradigms and offer a risk-free training environment (see for example Kuhn, 1997; Montgomery et al., 2001; Székely et al., 2000, and references therein).

Our current research aims at the development of a reference surgical simulator of highest possible degree of realism. This system will allow us to investigate the relationship between the degree of realism and the training effectiveness by reducing the fidelity of the high-end system gradually. Hysteroscopy will serve as the driving application for the implementation of this simulator. Hysteroscopy is a minimally invasive procedure performed on the uterus through the cervical ostium, i.e., the natural opening of the organ. It is the second most often performed procedure in gynecology after laparoscopy. Hysteroscopy allows for treatment of different pathologies under uterus saving conditions, which is especially important for women in their childbearing years.

One important advantage of VR based training is the possibility to confront the trainee with a broad range of different findings in a compressed period of time. For effective training of the procedures involved, it is eminent that the scene varies from session to session, thus challenging the person to be trained in every iteration and preventing any adaptation to the given implementation. Even so, the generation of variable surgical scenes has not yet been treated as a specific issue. Instead, today’s simulators use single
static organ models, usually derived from an exemplary anatomy such as an MRI dataset of a volunteer, or based on the Visible Human Project or artificially created with CAD systems.

The configuration of variable surgical scenes entails both the generation of variable models of the healthy organ as well as the incorporation of different pathologies and their instances. The variability of the healthy organ model has to capture the normal range of anatomical variance in the population of interest. The collection of pathology models should enclose the broadest possible range of different findings. The methods for the generation of these components are fundamentally different and will be discussed more in detail in Section 4. The focus of this paper is placed on tumor generation strategies based on growth processes, thus imitating the real emergence of these pathologies.

2. Pathologies in the uterine cavity

The pathologies investigated are (leio-)myomas and polyps protruding into the uterine cavity. Both pathologies are a common cause of dysmenorrhea, abnormal bleeding and infertility, and account for the majority of hysteroscopic interventions. While the symptoms and the appearance of these pathologies might be similar to some extent, their treatment during hysteroscopy is completely different. The proper treatment can follow from a correct diagnosis done at the beginning of the intervention.

2.1. Myoma formation

The prevalence of uterine leiomyomas is about 25–40% in women in their childbearing years. They are the most common benign tumors of the uterus in women over 35 years old (Heuck and Reiser, 2000). Myomas tend to be of spherical shape and their size can vary from a pearl to as large as a melon.

Myomas most often are classified into four types depending on their position relative to the uterine wall: first the intramural myoma, which is confined to the myometrium and referred to as such as long as it does not vault the endometrium or the serosa; second the submucosal myoma, which protrudes into the uterine cavity; third the subserosal myoma, which projects off the peritoneal surface of the uterus (Pschyrembel et al., 1990); and fourth the intraligamentary myoma, which protrudes into the surrounding ligaments. Both the subserosal and the submucosal myoma may be sessile or pedunculated and the latter can become prolapsed through the cervix into the vagina. Submucosal myomas are visible and treatable by hysteroscopy and therefore of main interest for the simulator.

Despite the amount of research performed in this area, the exact etiology of myomas is not known. It is assumed that the genesis is initiated by regular muscle cells with increased growth potential and that the growth of myomas is driven by estrogen (Pschyrembel et al., 1990). They are thus related to the function of the ovaries and neither appear before puberty nor emerge after menopause, when already existing myomas even tend to shrink. In general, they grow slowly but continuously until the beginning of the menopause (Netter, 1987). The increase of volume by a factor of two usually takes several months or years. Slow growing myomas tend to be squeezed out by the healthy surrounding muscular meshes. Therefore, they seem to migrate over months or years towards the inner surface (endometrium, submucosal) or towards the outer surface (serosa, subserosal). Since the myometrium is an active muscular mesh exhibiting slow waves of contractions, any tumor or foreign body affecting the uterine cavity will be extruded, probably leading once to a pedunculated myoma if not removed prior.

A myoma has a much stronger tendency to keep its shape than any of the tissues surrounding due to its very dense fibrotic tissue. This holds for the complete life-cycle of the pathology, i.e., for both the intramural and the submucosal myoma. The surrounding tissue consists of clustered myometrium. There is no separate capsule around the myoma. The tissue of the myoma as well as the surrounding tissue of the myometrium have a layered structure which often simplifies the resection of the myomas as they can be peeled off the myometrium (Pschyrembel et al., 1990). The visual appearance in the cavity is defined by the endometrium as it is a highly reactive tissue covering the whole uterine cavity as well as protruding myomas of any degree.

Removing a myoma is usually done by electric resection in small parts. A monopolar loop electrode is used to carve small stripes that can subsequently be grasped and extracted from the cavity through the cervix. It is crucial to keep the peduncle. Cutting off the peduncle of a myoma can lead to serious problems in hysteroscopy since the rigid sphere that forms the myoma will be floating like a ball in the cavity complicating any further extraction.

2.2. Polyp formation

Endometrial polyps are – like myomas – benign tumors. They are encountered most commonly in women between 40 and 50 years of age and occur relatively frequently after the menopause. Polyps are found in about 24% of the female population (Kurman and Mazur, 1990). As most polyps are small, they do not cause symptoms. Two types of polyps are distinguished, one originating from the corpus, the other from the cervix (Pschyrembel et al., 1990). There is no classification based on the size or shape of a polyp.

Polyps originate as focal hyperplasias of the basalis and develop into benign, localized overgrowth of endometrial tissue covered by epithelium. They contain a variable amount of glands, stroma, and blood vessels. These components make them – in contrast to myomas – very soft. Polyps may be broad-based and sessile, pedunculated, or attached to the endometrium by a slender stalk. Furthermore, they vary in size from 1.0 mm to a mass that fills...
and expands the entire uterine cavity. They rarely exceed 1.5 cm in diameter. Large polyps may extend down the endocervical canal or may even protrude into the vagina, being visible on physical examination. The surface is tan and glistening. Occasionally the tip or the entire polyp may be hemorrhagic or characterized by suffusions and petechiae due to irritation of infraction. Most polyps are solitary, but about 20% are multiple. They may originate anywhere in the uterine cavity, but most occur in the fundus, usually in the cornual region (Heuck and Reiser, 2000). The occurrence of carcinoma in benign polyps has been reported to be no more than 0.5%; however, polyps have been found in 12–34% of uteri with endometrial carcinoma. Polyps found in post-menopausal women are therefore always subject to histological investigation as they are often a side effect of a carcinoma (Bajka, 2001).

The hysteroscopic resection of a polyp – as opposed to the resection of a myoma – is best performed by picking the stem of the polyp and extruding it. It is important to remove any polyp completely from its basis. Otherwise, there will always be a chance of relapse. Once the polyp is separated from the uterus, it can easily be pulled out of the cavity since the soft tissue of the polyp can be squeezed through the cervix. If polyps and myomas cannot be visually distinguished, haptic feedback can indicate the type of pathology.

Hysteroscopy offers the advantage of direct visualization, targeted biopsy with simultaneous complete surgical resection of polyps and myomas. Ultrasound is not safe enough to accurately differentiate between polyps, hyperplasia and endometrial carcinoma. Hysteroscopy is more specific as a diagnostic tool in cases of post-menopausal bleeding and the combined use of hysteroscopy and biopsy leads to nearly 100% of accuracy (Savitha and Swapna, 2001).

3. Modeling requirements

A number of requirements have to be met by any pathology generation strategy to be suitable for surgical training simulators. The most important property of the resulting models is a realistic macroscopic appearance. This appearance is dominated by the shape and texturing of the surface representing the pathology, but extends to the biomechanical behavior and blood perfusion in the course of interventional simulation. The presented methods focus on the generation of realistic shapes while providing the necessary information for the additional components, so that correct properties can be assigned to the final results.

The implementation has to incorporate a wide range of variations in size, geometry, and position within one framework. Randomness is therefore introduced at different places to ensure a non-deterministic behavior of the models. The final goal is to provide a coherent scene consisting of the pathologies embedded into a healthy organ model. This can be achieved either by imposing boundary conditions to the growth process in the form of the organ model or by appropriate post-processing steps to ensure a seamless integration of the different components.

It is desirable to provide an intuitive set of parameters, if possible using medical terminology, to the end-user who will configure the different scenes. Common parameters are the type of the pathology, its size, and location within the healthy organ. Especially for the time consuming growth models, no user interaction should be necessary after the initialization. As no modifications of the tumor’s size or position are needed during the actual simulation of the intervention, the generation procedure can be computed prior to the training sessions.

Tumor growth has previously been modeled with different objectives in mind and a large body of literature proposing many different models is available (Cristini et al., 2003; Habib et al., 2003; Newman and Lazareff, 2003; Swanson et al., 2003; Zizzari et al., 2003). Mathematical models describing the temporal development of different factors that influence the growth of malignant tumors have received special attention. Most often research focused on malignant tumors in the brain. The investigated phenomena vary from sub-cellular to macroscopic scales. Subcellular processes are for example the chemical signals transmitted between cells. On the cellular level the proliferative rate of the single cells may be of interest while on a macroscopic scale the size and the biomechanical behavior of the tumor has been the focus of the investigations. The objectives of the different studies range from understanding of the general growth processes over the influence of single substances to the prediction of future development of patient specific cases, e.g., for the optimization of irradiation therapies.

The existing literature on tumor growth can be classified in (a) diffusion models, (b) continuum mechanics models and (c) cellular automata. Greenspan’s (1976) preliminary work on diffusion models focused on the processes involved in the first stages of tumor growth, i.e., so-called multicell spheroids, where diffusion of nutrients plays an essential role. The models are based on observations of in vitro experiments of cylindrical or spherical tumors. Adam (1986) proposed a one-dimensional model to investigate the stability of the growth process. The influence of angiogenic factors has been incorporated in the models of Chaplain (1996) to capture both the avascular and the vascular growth phase of solid tumors, therefore modeling the ability of a tumor to invade the surrounding tissue and metastasize to distant parts of the body. While very sophisticated models have been developed in the meantime, diffusion models in general neglect the mechanical interactions between the tumor and the surrounding tissue. Macroscopic, mechanical models of the tumor growth have been published more recently by Wasserman and Acharya (1996) and Kyriacou et al. (1999). The emphasis of these works were placed on a realistic deformation of the surrounding tissue and on the exact modeling of internal pressures. The finite element simulations included inhomogeneous material properties of brain tissues and were
A cellular automaton that implements the phenomenological description of the tumor growth by means of the Gompertz model has been presented by Qi et al. (1993). Later, Kansal et al. (2000) proposed a 3D cellular automaton to describe the growth dynamics of a brain tumor. The underlying lattice is a Delaunay triangulation where the density of the elements is allowed to vary, so that the growth speed is implicitly included in the initial configuration.

This non-exhaustive list of previous work done illustrates the large amount of modeling approaches investigated. While these publications propose interesting concepts for different aspects of tumor growth, none of them provides macroscopic findings that fulfill the application-specific requirements stated.

4. Modeling approaches

Different approaches for the generation of realistic macroscopic findings of the previously described tumors have been investigated in the context of the high fidelity surgical training simulator. The taxonomy of the underlying concepts is illustrated in Fig. 1. On a first level, one can distinguish methods that directly produce new valid instances of a desired tumor and methods that generate new cases in an iterative process starting from a given healthy environment. First the instance-generation methods will be discussed, followed by a detailed presentation of two approaches that imitate the growth process of pathologies.

Statistical shape analysis is a well established framework for the aggregation of knowledge from a set of geometric models and is commonly used for the incorporation of prior anatomical knowledge into the segmentation process (Cootes et al., 1995; Kelemen et al., 1999). Most often the underlying data is acquired by means of non-invasive imaging techniques such as MRI or CT and the models obtained by segmentation of the anatomical structures. In the case of the aforementioned pathologies, none of the available imaging techniques provide the fidelity needed for an accurate segmentation up to the level of detail observed by the gynecologists during intervention. In addition, the diversity of the pathologies, the amount of different findings and the temporal development of each of these tumors obviate a reasonable statistical analysis due to the amount of data required.

A possible implementation of an instance-generation methods is the skeleton-based design of tumors which has been presented earlier (Sierra et al., 2003). As has been realized by D’Arcy Thompson almost a century ago, axial growth processes play a decisive role in forming the shape of living objects (Thompson and D’Arcy, 1942). The related concept of local symmetries has later been shown to capture axial growth efficiently and can be handled by a coherent mathematical theory (Blum, 1967). In general, the skeleton of a three-dimensional object is a collection of connected 2D manifolds. In case of the investigated tumors, which show approximate rotational symmetry, the sheet based representation can be simplified to a single linear skeletal axis with an associated width function. The characteristic shape-profile of both polyps and myomas has been identified by visual inspection of intra-operative recordings, study of the related literature and discussions with medical experts. The profiles are parameterized by the control points of B-Spline curves and revolved around the skeletal axis. The number of parameters is further reduced by restricting the relative positions of the control points. Variation of the shapes is achieved by smooth, random distortion of the resulting surfaces at different resolutions. The final interactive implementation provides a few sliders on a graphical user interface that allow for an intuitive derivation of valid tumor models.

Methods that directly generate instances certainly allow for the fast derivation of a new sample. After its generation, the new instance has to be placed in an existing organ model. Additional processing is needed to merge the two independent components, tumor and organ, to form a coherent surgical scene. The complete procedure can be performed almost in real time on a standard PC, rendering this class of methods an attractive option for end-users.

Instance-generation methods are inherently unable to incorporate any physiological processes as they do not consider the history of single manifestations. A tumor will never grow independently from its surrounding and attach to a healthy tissue in an advanced stage (even malignant metastasis only occurs at cellular level, i.e., orders of magnitude smaller than macroscopic findings). These methods rather extract knowledge from a collection of existing cases at a given point in time.

In order to overcome this limitation of the described methods, the genesis of a tumor can be modeled, i.e., the process from the emergence of a single tumor cell to its macroscopic finding. This approach allows for the incorporation of physiological processes such as cell divisions for the representation of increased local growth rates. By approximating the actual growth process rather than a final status of a mature tumor, the algorithm can poten-
tially represent a much larger variation of shapes including those of intermediate stages. Two models that follow this idea have been implemented, namely a cellular automaton (CA) able to grow pedunculated, submucosal myomas and a particle based growth model that generates both polyps and myomas.

While ideally all processing steps are based on biological truth, current knowledge is far from providing all details for a complete simulation at arbitrary scales. Biological research focuses today mostly on the description of molecular features on the cellular level. Yet, the results of this research cannot explain the macroscopic findings of complete anatomical structures. Medical science is either interested in the gross anatomical description of observed abnormalities or on specific characteristics at the cellular level such as mitotic indices. The scales in between these two extremes have largely remained unexplored.

The investigated pathologies consist of millions of cells which is more than can reasonably be represented today in any computer simulation. In order to establish a reasonable balance between tractability and accuracy of the model, the elementary units of the simulation approaches presented (i.e., the actual state of a node of the cellular automaton or a particle) has to be related to a cell conglomeration rather than to a single cell.

5. Cellular automaton implementation

The implemented CA comprises two cell types and the background or cell-free space. The first cell type is the tissue which consists of the muscle cells of the myometrium, the second cell type represents the tumor cells. The background describes the uterine cavity.

The CA is defined by a regular, three-dimensional, cubic lattice. The neighborhood template \( N^7 \), a set of elementary states \( \mathcal{E} \), and local, space- and time-independent transition rules \( \mathcal{R} \). The local rules are either probabilistic or deterministic (Dormann, 2000).

In the following, the term node is used to refer to the cells of the automaton to avoid confusions with biological cells. A node is specified by its position \( p = (i,j,k) \) in the lattice. The neighborhood template \( N^7 \) specifies the nodes that influence the state of the node under scrutiny. \( N^7 \) is rule dependent and can be either a 6-neighborhood (\( N^6 \), von Neumann neighborhood) or a 26-neighborhood (\( N^{26} \), Moore neighborhood). Whenever possible, the smaller neighborhood is selected.

The set of elementary states \( \mathcal{E} \) for the tumor is upper bounded by \( J \) and defined as a multiple of the step \( \Delta = \frac{1}{c} \). Each node has a tumor component with a certain probability \( p(p) \) if its neighbors in \( N^7 \) has a tumor component. The equation for \( \mathcal{R} \) is equivalent to a linear proliferation but restricted to produce geometrically correct shapes, i.e., grow spherical patterns. The following observation illustrates the approach to identify suitable probabilities. If \( p(p) \) is set to 1 in the direct neighbors in \( N^{26} \), a square with 45° rotation will be generated. If \( p(p) = 1 \) in all elements of \( N^{26} \), a volume-aligned square will emerge. In order to approximate a spherical shape, numerical experiments have been performed to find optimal probabilities for the neighbor selection. We have observed that already small deviations from the purely \( N^7 \)-based scheme \( p_{\text{direct}} < 0.99, p_{\text{diag}} > 0.05, p_{\text{corner}} > 0.05 \) lead to approximately spherical tumor formation. In contrast, a more pronounced preference of non-direct neighbors \( p_{\text{direct}} < 0.8, p_{\text{diag}} > 0.2, p_{\text{corner}} > 0.2 \) closely resembles the outcome of the homogeneous \( N^{26} \) scheme while rounding off the corners of the resulting cube. Accordingly, \( p_{\text{direct}} = 0.9, p_{\text{diag}} = p_{\text{corner}} = 0.1 \) has been selected in all experiments. Once a tumor component is in a node, it is continuously incremented by \( \mathcal{R}_{\text{grow}} \). Three objectives are modeled with this rule; the spherical shape of the myoma, the inhomogeneity of the surface, and the reactive shell around the tumor.

The migration of the myoma is related to the relative position of the tumor in the tissue. Therefore, a global cost function of the current tumor position is computed. For all nodes with a tumor component the amount of tissue in the same node is accumulated to an overall cost \( C_8 \). The complete tumor is then translated by one cell into the six directions \( d_i \) given by \( N^6 \) and the same cost function is evaluated separately for every direction \( d_i \) resulting in six
additional cost values $c_i$. The rule $R_{\text{moving}}$ then moves the tumor into the direction $d_{\text{opt}}$ corresponding to the optimal cost $\min(c_i)$, which represents the translation of the tumor into the direction of the tissue concentration gradient.

$$R_{\text{moving}}: c_{\text{tumor}}(p)_{t+1} = c_{\text{tumor}}(p - d_{\text{opt}})_t$$

Note that the complete tumor is homogeneously translated, thus keeping a compact spherical structure. Therefore, the rule represents purely the repulsive behavior of the healthy tissue. A third rule $R_{\text{adaption}}$ models the adaption of the surrounding tissue to the new situation. In a first step, the displacement of the tissue introduced by the growing tumor is encoded. This rule uses the incremental property of $R_{\text{grow}}$

$$c_{\text{tissue}}(p)_{t+1} = \min\left(1, c_{\text{tissue}}\left(\arg\max_{q \neq p} c_{\text{tumor}}(q)\right)_t + c_{\text{tissue}}(p)_t\right)$$

$R_{\text{adaption}}$ changes the tissue concentration in the proximity of the tumor, which is therefore a good representation of the clustered myometrium observed around the myomas. This rule will influence the cost functions $c_i$, evaluated in the subsequent iterations. In a second step of $R_{\text{adaption}}$, the displacement is propagated into the surrounding area by smoothing the tissue state. While this could be represented by an additional rule, Gauss filters of variable width are used in the actual implementation for simplicity. This relaxation of tissue may have to be applied several times to ensure that the endometrium always covers the tumor.

The global rule $R_{\text{global}}$ defines which of the rules $R_i$ is applied in one iteration. $R_{\text{global}}$ is time dependent so that the applied sequence of rules $R_i$ changes during evolution. This allows for example to model a faster movement of the tumor while it is small. As the tumor size increases, the rule $R_{\text{moving}}$ is applied less often to model a slower motion. As soon as the tumor is pedunculated, this rule can again be applied more frequently. By counting the number of applications of rule $R_{\text{grow}}$ and multiplying this number with the respective probability for $N_{\text{eq}}$, it is possible to keep track of the tumor’s volume, so that the growth can be stopped at a user specified tumor size.

The organ models are provided as surface meshes that have to be combined with the resulting tumors. The transformation of the surface mesh into a voxel based representation inherently loses information as the original surface mesh cannot be accurately reconstructed. Therefore, only a small region of growth is converted from the organ model to the voxel representation and the tumor growth is restricted to this domain (Sierra et al., 2003).

A fundamental limitation of cellular automata is the inability to differentiate nodes with the same components, i.e., two adjacent nodes have no information whether they belong to the same or different fragments of the endometrium. This limitation rules out any incorporation of collision handling into the growth process. As is illustrated in Fig. 2, it is not possible to distinguish the healthy tissue around the myoma’s core and the surface of the organ.

The presented CA is therefore limited to model spherical growth patterns and is bound to stiff tumors that grow almost independently of the surrounding tissue. While this assumption is reasonable for myomas, it is certainly not true for polyps, as their shape is strongly influenced by the cavity.

6. Particle based growth model

The particle based growth model allows for the generation of both polyps and myomas. The models are directly computed in the organ’s domain rendering an explicit integration of the tumor into the organ model obsolete. Particles $p$ are used as entities in a three-dimensional space which carry constant (e.g., size represented by a radius $r$, mass $m$) and time-dependent attributes (e.g., position $x_p$, and forces $F_p$). In the following, the subscript denotes the type of the particle and the superscript denotes the index.

The use of particles without fixed connections for the representation of tissue development is motivated by current knowledge of morphogenesis. Mechanical forces are generated by the dynamic rearrangements of cell–cell contacts and the cytoskeleton. Research in the field has revealed that the cell shape and motility are influenced by these forces leading to the transformation of uniform sheets of cells into specialized three-dimensional structures. During morphogenesis, groups of cells remain cohesive while other intercellular and substratum connections are selectively disassembled (Jamora and Fuchs, 2002).

Each particle interacts with its current neighbors based on a radial-symmetric force profile, which relates the distance $r_{ij}$ between the particles $p'$ and $p'$ to a force $F_i$. The function $f$ relating the distance $r$ to a force $F(r)$, $f: \mathbb{R} \rightarrow \mathbb{R}$ has to emulate the intercellular behavior during morphogenesis. The group of monotonically decreasing and positive functions will only be able to model repulsion of particles thus increasing the inter-particle distance. To represent the tensile and compressive forces acting on cells, the function $A_2$ defined by:

$$A_2: \quad F(r) = \begin{cases} 0 & : r > \frac{3}{2}r_0 \\ \frac{1}{2} \left(1 - \frac{r}{r_0}\right) \left(2 - \frac{r}{r_0}\right) & : \frac{1}{2}r_0 \leq r \leq \frac{3}{2}r_0 \\ \frac{2}{3} - \left(\frac{r}{r_0}\right)^2 & : 0 \leq r \leq \frac{1}{2}r_0 \end{cases}$$

was empirically selected from the literature (Cottet and Koumoutsakos, 2000). $r_0$ is the closest equilibrium distance between two particles where $F(r_0) = 0$. Particles interacting
with a $A_2$ force profile arrange themselves in a regular grid with a preferred inter-particle distance $r_0$. The selected function has discontinuities for $r = \frac{1}{2}r_0$ and $r = \frac{3}{2}r_0$. The cut-off at $r = \frac{3}{2}r_0$ prevents a slow and incremental influence of neighboring particles. The discontinuity at $r = \frac{1}{2}r_0$ can be seen as a penalty for a too close approach whereas any function which tends to infinity for $r = 0$ would result in an extremely unstable simulation. Image (a) in Fig. 3 shows the graph of the $A_2$ function.

In contrast to the simulation of organs when performing surgical tasks like cutting, growth models of tissues have to be based on static equilibriums rather than on dynamic simulations. There is no meaningful interpretation of a cell velocity or even an acceleration in the investigated processes. Therefore, all simulation steps performed in the current algorithm aim at a new equilibrium state after every growth iteration. Updating the particle’s position is thus based on a quasi-static solution of the Euler integration scheme

$$\ddot{x} = \frac{F(r)}{m}$$

that can easily be obtained by selecting a high damping coefficient $\gamma = \frac{h^2}{\bar{\theta}}$ in the classical Euler differential equation solver.

Three different types of particles are used in the algorithm. The myometrium or healthy tissue is represented by a constant number of particles $p_{\text{tissue}}$ distributed randomly in the corresponding region defined by the organ anatomy. The pathology consists of one initial particle $p_{\text{tumor}}$, with similar properties to the tissue particles. The single difference is that tumor particles have the ability to divide themselves, modeling the increased mitotic index of tumor cells. The endometrium is represented by particles $p_{\text{endo}}$ which are interconnected by triangles to build an impermeable membrane for all other particles. The edges of the triangles are represented by springs to allow for limited deformations of the surface. Thus the vertices of the surface mesh of the organ can directly be used as initial particles $p_{\text{endo}}$. The different tissues are illustrated in image (b) of Fig. 3.

Equivalent to the CA, the algorithm consists of a main growth loop which is iterated until the desired final stage of the tumor is reached. The governing equations have been heuristically defined in order to be in accordance with the observed phenomena. In every iteration the following operations are performed:

1. tumor particle division;
2. tissue adaptation;
3. surface adaptation;
4. surface fairing.

The tumor is initialized as a single particle $p_{\text{tumor}} = \{p^0_{\text{tumor}}\}$ whose location can be selected interactively. As mentioned, polyps originate from a local overgrowth of the endometrium. Thus, a vertex of the uterine surface mesh has to be chosen. For myomas, any tissue particle can be selected and converted to a tumor particle as they originate from the myometrium.

1. Tumor particle division. Tumor cells have increased proliferative rates causing the abnormal growth. This is the only active process in the algorithm in contrast to the following steps that are reactions to this particle division. Two different rules are used depending on the type of pathology. In case of a polyp, the same initial particle will be divided in every iteration:

$$\mathcal{R}_{\text{dividepoly}} : p^0_{\text{tumor}} \rightarrow \{p^0_{\text{tumor}}, p^{0+1}_{\text{tumor}}\} \quad n = \|p_{\text{tumor}}\|$$

where $\tilde{n}$ denotes the normal vector of the surface. The new particle is pushed slightly inside the tissue to ensure that it will not fall outside the endometrium. As $\delta \ll r_0$, the following operations will push the new particle further into the tissue.

In case of a myoma, all tumor particles are equally able to divide. A tumor particle $p^i_{\text{tumor}}$ is randomly selected and divided:

$$p^i_{\text{tumor}} \rightarrow \{p^i_{\text{tumor}}, p^{i+1}_{\text{tumor}}\} \quad i = \text{RAND}(0, n)$$

where RAND is the uniform distribution. The vector $r_0$ is uniformly distributed over the surface of the sphere with radius $r_0$. Details about the computation of such a vector

![Fig. 3. (a) $A^2$ profile. (b) Transparent view of a polyp, see also Movie 1. The different tissues are represented as follows: the wireframe surface is the endometrium, particles in grey represent one layer of myometrium and the dark particles label the tumor. (c) Topological operations on triangles used for endometrial surface fairing.](image-url)
can be found in Marsaglia (1972). This specific distribution ensures a global spherical growth pattern while using only local operations. Given an equilibrium inter-particle distance of \( r_0 \), the factor 0.5 places the particles \( i \) and \( n + 1 \) at the optimal distance with respect to each other, but closer to surrounding particles, thus ensuring a reaction of the neighborhood in the following rule.

2. Tissue adaptation. The new particle as well as the fairing of the surface in the previous iteration change the force felt by almost all particles. Each particle accumulates the forces acting on itself from the subset of close enough particles, that is \( r_{ij} \leq \frac{1}{2} r_0 \):

\[
\vec{F}^t_{pi} = \sum_{j \in \Phi} F(r_{ij}) \frac{\vec{r}_{ij}}{|\vec{r}_{ij}|}
\]

(2)

Based on the force, the particle is translated using Eq. (1). The time step \( h \) has to be selected small enough to prevent particles from outrunning each other. Intuitively, the positions would only be updated after all particles have accumulated their respective forces. For small changes, i.e., small values of \( h \), the convergence is faster using serial computation, that is every particle \( p' \) is updated based on Eqs. (2) and (1), and following particles \( p', j > i \) are updated based on the new positions \( x_{p'}^{t+1} \).

To handle collisions of the pathology’s surface with the uterine cavity, an additional interaction between the tumor particles and the organ’s surface particles is added at this point. Each particle has to add an additional term into Eq. (2) originating from the organ’s surface. As opposed to the \( A_2 \) profile, the interaction profile has to be purely repulsive to mimic the collision, i.e., \( F(r) \geq 0 \forall r \). An algebraic function \( F(r) = \frac{1}{r^3} \) has been selected, as it decays relatively fast and thus limits the range of influence. However, the specific choice is not crucial for the simulation and other monotonically decreasing, upper bounded and positive functions can be used.

3. Surface adaptation. The surface’s shape is adapted according to the tumor’s deformation as the endometrium is always covering all tissues. All particles apply forces on the surface, again as a function of the distance to it. In this processing step it is crucial to compute exact distances from the particle to the surface and not just to the vertices of the surface, as particles may otherwise penetrate the triangular mesh. The resulting force on a triangle \( \mathcal{T} \) is transferred to the three vertices of \( \mathcal{T} \). After the accumulation of the external forces, the surface springs are relaxed. As for the particles, the stationary equilibrium of all springs is approximated. The surface can be deformed in almost arbitrary directions by the growing tumor. Additional steps are therefore taken to ensure a smooth behavior of the mesh.

4. Surface fairing. Adaptive subdivision is introduced to mimic the actual growth of the endometrium. The set of triangles \( \mathcal{T} \) with an area larger than a threshold \( t \) is subdivided using quaternary subdivision. The remaining triangles are subdivided if they are adjacent to a triangle of \( \mathcal{T} \) to ensure a correct triangulation of the complete mesh. Quaternary, A-shape and T-shape subdivision is applied, depending on the number of adjacent triangles that have been subdivided. Image (c) in Fig. 3 illustrates the different topological operations.

Following the subdivision, the quality of the triangles is enhanced by edge swapping. The ratio of the inscribed circle radii is used as quality measure, as it is faster to compute than other measurements and has been shown to have only one stationary value for the equilateral triangle (Pébay and Baker, 2001): \( \rho_q = \frac{q_{\text{inc}}}{q_{\text{circ}}} \)

For any two neighboring triangles, the common edge is flipped if \( \rho_q > \rho_{q_1} + \rho_{q_2} \). Finally, small triangles are removed by collapsing the shortest edge of the triangle. To ensure topological correctness, this operation is only applied in a conservative manner, i.e., if the involved vertices as well as their common neighbor vertices all have valences larger than three (Quicken et al., 2000).

After fairing of the surface, all springs are assigned a new equilibrium length corresponding to the current length and all external forces are deleted. This concludes the transition into a new stationary equilibrium of the growth process.

7. Results and discussion

The algorithms presented produce both realistic shapes of the investigated pathologies and fulfill the requirements stated in Section 3. An exemplary growth sequence for a myoma using the CA is shown in Fig. 4. The growth domain consists of a lattice of 100\(^3\) nodes. \( \Lambda \) was set to 0.1 and the tissue concentration ranged from 1.0 to 0.1 towards the surface, i.e., a gradient of \( \frac{\partial c}{\partial q} = 0.03 \) has been selected. A stronger decay will move the pathology in each iteration towards the cavity. Omitting the gradient will result in a stationary tumor that will eventually start to migrate into the cavity after vaulting the uterus-cavity boundary, as the tissue will be slowly thinned at this stage. All parameters can be specified by the user and will influence the relative size of the pathology in the given domain and the relative speed of migration versus growth. The probabilities \( p(q) \) suggested for the growth pattern are scale-invariant and can only be slightly modified for the correct representation of myomas. If desired, elongated structures can easily be generated by anisotropic specification of the probabilities. Both the inner stiff core and the surrounding tissue are visualized. This differentiation provides the necessary information for further processing, i.e., for the incorporation of vascularization models or the definition of various biomechanical properties.

A resulting growth sequence for the particle based method is depicted in Fig. 5, where a polyp embedded in the fundus of a uterine cavity is grown. In the image sequence, the camera moves from the right tubal ostium towards the cervical channel. It can be observed how the polyp is deformed by the shape of the cavity between the second and the third image. The organ anatomy used in this example has been derived from the Visible Human Female project (Bajka et al., 2004). However, the growth
process can be initialized on any triangulated surface mesh. As can be seen in Fig. 5, the triangulation has been refined in the proximity of the pathology on initialization. The growth behavior is sensitive to the correct relative parameter settings and the overall size of the domain, i.e., the equilibrium distance \( r_0 \) of the particles has to approximately match the equilibrium spring length on the surface and has to be significantly smaller than the diameter of the polyp to be generated. In the presented example the cavity has a depth of approximately 70 units and \( r_0 \) has been set to 1.25. The time step \( h \) and the mass \( m \) of the particles are 1.

The spring stiffness \( k \) on the surface is crucial for the well-behaved deformation and growth of the pathology. If \( k \) is set too stiff, the surface will not allow the tumor to grow and force particles to escape through the wall. A value of 0.5 was set in the shown example. In order to limit the computational burden, in case of polyps a single layer of particles at the equilibrium inter-particle distance, generated parallel to the surface is sufficient to represent the myometrium. While the identification of proper parameters requires several experiments, the same set can be used to generate unlimited pathologies for a specific organ model, as the variability is introduced solely by the selection of the tumor seed and the cavity’s shape.

A visual comparison of intra-operative images of both a polyp and a myoma with their respective virtual counterparts is provided in Fig. 6, images (a)-(d). In order to provide comparable scenes, the surfaces have been manually textured with image fragments extracted from the intra-operative recordings. The results demonstrate the high resemblance of the results to real cases, achieved by tumor growth and texturing. The following paragraphs compare the basic properties for the CA and particle method. A summary of these properties is provided in Table 1.

7.1. Discretization

In a CA, both space and time are discrete variables which are favorable properties for computer based simulations. Computational stability is intrinsically a part of cellular
automata (Dormann, 2000). The main advantages of cellular automata are the simplicity and extendibility of the implementation. Rules can easily be added, removed or modified.

The particle method has a continuous representation of space, as the single particles are free to move. The careful selection of the different parameters such as maximal forces and time steps is therefore crucial for a stable simulation. On one side, the accumulated forces should not become too large to prevent penetrations of the surface mesh for example. On the other side, the time steps should not be too small to limit the time required for the generation of a new pathology instance.

7.2. Neighborhood connectivity

As cellular automata have a fixed neighborhood connectivity, the rules can be evaluated by directly accessing the relevant nodes. Therefore the computational time for one iteration is of the order of $O(m)$, where $m$ is the number of nodes. As the size of the domain does not change from one iteration to the other, the time required for one growth step is constant over the complete simulation.

On the contrary, the computation of all distances between all particles is in principle necessary for the evaluation of the inter-particle forces. This process requires $O(n^2)$ steps in a straightforward implementation where $n$ is the number of particles. It has been shown that this can be reduced to $O(n \log n)$ by using optimization techniques such as the spatial sorting of particles (Barnes and Hut, 1986). New particles and triangles are generated as the algorithm progresses, so that the single iterations become more time consuming as the tumor grows.

7.3. Simulated time resolution

The single iteration in the CA represents a relatively large time interval, so that an advanced tumor size can be reached in only about 50 iterations, as illustrated in Fig. 4. The overall procedure can be computed in roughly 1 min on a standard 3 GHz PC.

The particle method has a higher resolution in time. The example in Fig. 5 shows the progress over 400 iterations computed in about three hours.

7.4. Variability

In the case of the CA, the randomness of the final results originates from the probabilistic application of the rules. The single rules are applied in a strict sequential order.

In the particle method, the rules are applied in a deterministic sequence. The random spatial distribution and displacements introduce the variability, which is further influenced by the healthy organ’s anatomy. The particle method combines sequential and synchronous updates; the particle’s positions are updated in a sequential order while the surface is only adapted after the accumulation of the distinct forces.

The validation of the resulting tumor instances is necessary for the further use of the models in a realistic training environment. Different levels of validation can be identified and various aspects within the different modeling techniques can be validated. Ultimately, in the context of surgical training simulators, the patient’s outcome and the number of complications must be the target measurements. Such a patient oriented validation is envisioned as soon as the complete simulator is operational and can be used to train medical residents at different levels of fidelity. Nevertheless, a system oriented validation is crucial to exclude any adverse effects of training due to wrong information provided to the apprentices. Therefore, a more appropriate aspect to be investigated in the context of model generation is the specificity of the grown structures, i.e., how accurately they are able to represent reality.

The models can be inspected at different scales. First, the overall appearance of the different shapes can be evaluated. The single steps to generate them can be analyzed. The pri-
mary goal in this context is to prove that the generated shapes are plausible examples of real cases. Growth models such as the ones presented are not designed to reproduce patient specific tumor instances. Even if the exact evolution of the patient’s tumor would be known, the probabilistic nature of the growth process would prevent the reproduction of a specific growth pattern. Therefore, the objective is to extract different geometrical properties of the investigated pathologies (e.g., the size of the peduncle) from existing cases which can provide a probabilistic ground truth for validation of the models presented.

Despite the amount of research, the exact etiology of the investigated pathologies remains unknown. To the best of our knowledge, there are no publications that provide exact metrics of the discussed pathologies beyond the gross description of type and extensions (for examples of the latter see Preutthipan and Herabutya, 2004; Pérez-Medina et al., 2005). Both ultrasound and MR imaging fail to provide data of sufficiently high resolution to exactly estimate shape details. The pathologies themselves are completely destroyed upon removal, thus preventing a direct measurement of the resected pieces. Ethical considerations clearly rule out influencing the therapy selection by the need of clinical studies aiming at the quantification of the tumor shapes. Therefore, intra-operative recordings remain the only non-invasive imaging technique that can potentially provide the level of detail necessary for an accurate surface description. The endoscopic perspective of the operation site still poses many challenges for an accurate 3D reconstruction of the scene. The camera provides highly distorted images with partial occlusions at variable focal lengths of a non-rigid scene, i.e., both cavity and tumors may change their shape and position during the inspection. Nevertheless it has been shown that the reconstruction of shapes from uncalibrated motion is feasible (Hartley and Zisserman, 2000). First results for the estimation of the volume of the cavity based on one specific recording are promising, but also revealed many challenges that have to be solved for a complete scene reconstruction.

An alternative validation method is the qualitative evaluation of the results. While this approach is certainly subjective, the clinician’s judgment will implicitly incorporate the cumulative variability of different findings. Therefore, experts have been provided with realistically textured examples to judge their plausibility based on their personal experience. Also, the growth patterns have been evaluated and the attention of the clinicians drawn on various aspects such as size, curvatures, pedunculation, and overall scene impression. The results provided the fidelity expected from the medical experts, which are therefore suitable models for the use in surgical training simulators.

8. Conclusion and future research

Different approaches for the generation of pathology models specifically designed to meet the requirements of an advanced surgical training simulator have been presented and evaluated. Growth models are in general superior to direct instance-generation methods as they allow the incorporation of biological knowledge, thus increasing the specificity of the methods. From the presented methods, the particle based model proved to be very sophisticated and allows for the incorporation of many different factors that influence the growth behavior. The combination of the particle system theory with an explicit surface representation opens the way for a versatile modeling of the macroscopic phenomena of tumor growth. As the method is very general and does neither impose spatial nor algorithmic restrictions, it has to be seen as the most promising approach for realistic tumor growth models.

While the visual inspection proves that the methods produce valid instances, it remains an open question how accurately the simulations are. Future research will be twofold. On one side the specificity of the models will be increased by extending the number of factors involved in the growing process. On the other side, the extraction of metrics from intra-operative recordings will be further evaluated. We are currently extending the particle based method with vascularization models to investigate the influence of angiogenic factors on the tumor growth. In a next step, mechanical factors such as friction will be added.

Preliminary results in two dimensions have shown that myomas can be modeled with the same basic rules, but require a much larger number of particles to represent the healthy tissue. Even though no real-time computation is needed for the generation of the models, the more than linear increase of computational power needed for the evaluation of all particle interactions renders this simulation impracticable. Therefore, optimization techniques such as the spatial partitioning have to be implemented for the modeling of myoma growth.

Certainly the concept can be extended to represent other growth patterns. An interesting area of research is the growth of malignant tumors which tend to invade surrounding tissues and even metastasize into distant locations. In combination with vascular models, the latter effect might even lead to significant insights into the involved processes.

The fidelity of the provided results has been judged sufficient by clinical experts in order to provide a highly realistic surgical training environment. Combined with methods to generate variable healthy anatomical structures (Sierra, 2004), the resulted methods are being integrated into a first prototypical simulator environment. Clinical trials of the complete system including dedicated force-feedback devices and realistic blood flow simulations are expected in the near future. The final simulator will allow us to evaluate the training effect of the different pathology models.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.media.2005.11.004.

References


