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Medical Image Segmentation: Energy Minimization and Deformable Models

Chris McIntosh and Ghassan Hamarneh

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This chapter surveys the field of energy minimization as it applies to medical image segmentation (MIS). MIS remains a daunting task but one whose solution will allow for the automatic extraction of important structures, organs, and diagnostic features from medical images, with applications to computer-aided diagnosis, statistical shape analysis, and medical image visualization. Several classifications of segmentation techniques exist, including edge-, pixel-, and region-based techniques, in addition to clustering, and graph-theoretic approaches (Pham et al., 2000; Robb, 2000; Sonka and Fitzpatrick, 2000; Yoo, 2004). However, the unreliability of traditional, purely pixel-based methods in the face of shape variation and noise has caused recent trends (Pham et al., 2000) to focus on incorporating prior knowledge about the location, intensity, and shape of the target anatomy (Hamarneh et al., 2001). One type of approach that has been of particular

interest to meeting these requirements is that of energy minimization methods due to their inherent ability to allow multiple competing goals to be considered.

In energy minimization methods, a function evaluates the goodness of a segmentation for a particular image, and the minimization of that function yields the segmentation of the image (Figure 23.1). Though highly variant in nature, the application of energy minimization methods to MIS is commonly built on five primary building blocks: (i) the energy function, (ii) the

FIGURE 23.1
A corpus callosum (CC). (a) The CC is the band of nerve fiber tissue connecting the left and right hemispheres of the brain. (b) An energy minimization segmentation process. A shape model with progressively lower energy (left to right), showing a minimum of the energy function in bottom right. (Adapted from McIntosh, C. and Hamarneh, G., Vessel crawlers: 3D physically-based deformable organisms for vasculature segmentation and analysis, *IEEE Computer Society Conference on Computer Vision and Pattern Recognition*, 2006, Vol. 1, pp. 1084–1091, 2006a; Hamarneh, G. and McIntosh, C., Physically and statistically based deformable models for medical image analysis (Chapter 11), *Deformable Models: Biomedical and Clinical Applications*, pp. 335–386, 2007.)

segmentation representation, (iii) the image representation, (iv) the training data, (v) and the minimizer. In what follows we provide an overview of each building block, and the major works therein over the past few decades.*

23.1 Definitions and Foundations

We first give an outline of the energy minimization for MIS process. We define a medical image I_i and its corresponding segmentation (i.e., pixel labels) S_i , each having N pixels. Then $\mathbf{I} = \{I_1, I_2, \dots, I_N\}$ and $\mathbf{S} = \{S_1, S_2, \dots, S_N\}$ are sets of images and their corresponding ground-truth segmentations. In a slight abuse of the notation, we occasionally omit the subscript i from I_i and S_i for clarity and instead use I and S .

The first step in any energy minimization problem is the identification of the form of the energy function. In the next section, we will briefly group some popular energy terms into three main categories: boundary, region, and shape. Boundary terms are concerned primarily with the object boundary, region terms with the region inside or outside the object, and shape terms with the shape of the object. Other energy terms include spatial constraints on multipart objects, for example, containment (or layering), exclusion, or the number of labels (DeLong et al., 2012; Nosrati and Hamarneh, 2013; Ulen et al., 2013; Yazdanpanah et al., 2011). Here we use these groupings to build a general energy functional. It may be convex or non-convex, as can the shape space over which it will be minimized. A general form is $E(S, I, \mathbf{w}) = w_1 \times \text{boundary}(S, I) + w_2 \times \text{region}(S, I) + w_3 \times \text{shape Prior}(S)$, with free parameter $\mathbf{w} = [w_1, w_2, w_3]$. Depending on the value of $\mathbf{w}$, minima of E tend toward best satisfying the boundary, region, or shape terms. We note that the boundary and region terms are often referred to as external terms, since they involve cues external to the shape model, while the shape prior is deemed an internal term. More generally, we can write

$$E(S, I, \mathbf{w}) = w_1 J_1(S, I) + w_2 J_2(S, I) + \dots + w_n J_n(S, I), \quad (23.1)$$

where

J_i is the i th energy term

$\mathbf{w} = [w_1, \dots, w_n]$ are the weights

We note here that depending on the nature of S , E may be called an energy function or an energy functional, with the latter indicating S itself is a function.

The segmentation problem is to solve

$$S^* = \arg \min_S E(S | I, \mathbf{w}), \quad (23.2)$$

which involves choosing a $\mathbf{w}$ and, depending on the nature of the energy functional, may also require training appearance and/or shape priors using

* This chapter summarizes and builds upon McIntosh (2012).

I and/or **S** and setting an initialization. A gradient-descent-based solver is typically used but combinatorial approaches have also been explored for discretized versions of the problem (Boykov and Kolmogorov, 2003) (see Section 23.5 for details). In either case, non-convexity, or supermodularity for combinatorial problems, can be quite problematic. There is no guarantee that another solution does not exist that better minimizes the energy and thus is potentially a better segmentation (Figure 23.2). Ideally both functional and shape spaces are convex, guaranteeing globally optimal solutions. However, whether convex or not the ground-truth segmentation, S_i , for image, I_i is not guaranteed to be an optima (local or global) of $E(S | I_i, \mathbf{w})$. The goal, in general, is to build an $E(S | I_i, \mathbf{w})$ such that S^* is as close as possible to S_i under some definition of closeness [e.g., (Dice, 1945; Jaccard, 1901; Tanimoto, 1957)].

One of the earliest developed, and perhaps most recognized, examples of energy minimization methods being applied to image segmentation is that of deformable models. Deformable models for MIS gained popularity since the 1987 introduction of *snakes* by Terzopoulos et al. (Kass et al., 1987; Terzopoulos, 1987). At a high level, energy-minimizing deformable models work by deforming a user provided initial shape to fit to a target structure in a medical image. Shape-changing deformations result from the minimization, with respect to the shape, of a cost function measuring how plausible is the shape model and how well it aligns with the boundaries of the target anatomy in the image. Since the shape model itself is most commonly represented by a function, the cost function is often termed an energy functional and its gradient is derived using methods from variational calculus. The shape deformations are therefore typically simulated by solving an initial value problem using gradient-descent optimization algorithms (Elsgolc, 1962, G2). One further development, “Deformable organisms,” uses artificial life modeling techniques to augment the energy-minimizing deformable models with models of cognition, behaviors, and sensory input (Hamarnah et al., 2001, 2009).

We now begin our more in-depth discussion of the different components of the energy minimization for MIS process.

23.1.1 Energy Function

Since snakes paved the way, there have been numerous papers attempting to increase accuracy by contributing novel energy terms, each designed to address a particular class of images or alleviate a particular problem with the original terms. As there have been far too many proposals to survey them all, here we focus on the key terms, many of which themselves have spawned numerous new approaches to MIS or changed the way we think about the problem at hand. As much of the initial development focused on external energy terms, namely, on the boundary and region terms that deal with the image processing itself, we begin our discussion there.

One of the most fundamental problems noted with snakes relates to their boundary capture range. If placed near a strong edge in an image, the

FIGURE 23.2

Synthetic example of single parameter deformable model with local minima. The circular deformable model's only parameter is its radius r . The energy function $F(r)$ is minimal for the circle with darkest average intensity. The input image is shown in (a) with the darkest outmost boundary representing the global minima. In (b) two deformable models are initialized. In (c) after gradient descent, each model has moved to the nearest minima. (Reprinted from McIntosh, C., *Energy functionals for medical image segmentation: Choices and consequences*, PhD dissertation, Simon Fraser University, Burnaby, BC, Canada, Copyright 2011. With permission.)

contour would quickly *snap* to the edge, but if initialized farther away the influence of the edge would not reach the contour. There are, in fact, numerous causes of this problem relating to not only the external energy terms (Caselles et al., 1997; Cohen, 1991; Xu and Prince, 1998) but also the way the segmentation was originally represented (an explicit contour—see Section 23.1.2 for details) and the minimization technique being used.

An early attempt to rectify the aforementioned problem was by adding a deflation or inflation force to the contour that would attempt to shrink/grow it toward edges (Cohen, 1991). Rather than rely on a constant force, gradient vector flows extend the influence of edges off into homogeneous regions, thus increasing the capture range (Xu and Prince, 1998). Geodesic active contours (GACs) were similarly developed by both Caselles et al. (1997) and Yezzi et al. (1997). The approach of Caselles et al. formulated a deformable model optimization problem as that of finding the optimal path in a Riemannian space. Termed GACs, these popular deformable models work by minimizing curve length, where length is measured as the geodesic distance on a Riemannian manifold defined via an edge indicator function. The shortest curve is then, by definition, the curve along the edges of the image, and thus GACs automatically shrink the curve to the edges. GACs have become the canonical example of boundary-based deformable models.

However, what about objects whose boundaries blurred due to their inherent nature or noise, like the example in Figure 23.3? In these cases the intensity statistics of the areas both inside and outside the contour can be used to attempt to divide the image into maximally separated regions. The approaches

FIGURE 23.3

An energy minimization segmentation process. A shape model with progressively lower energy (left to right), showing a minima of the energy function in bottom right. Notice the leaking into neighboring structures that occurs as a result of weak edge strength. (Reprinted from McIntosh, C. and Hamarneh, G., 2006b, Genetic algorithm driven statistically deformed models for medical image segmentation, *ACM Workshop on Medical Applications of Genetic and Evolutionary Computation Workshop (MedGEC), in Conjunction with the Genetic and Evolutionary Computation Conference (GECCO)*, Seattle, WA, 2006b. With permission.)

of Chan et al. and of Yezzi et al. (Chan and Vese, 2001; Tsai et al., 2001) were similarly developed. Both are modeled after the Mumford–Shah functional wherein images are approximated by piecewise-smooth functions (Mumford and Shah, 1989). The approach of Chan and Vese is referred to as active contours without edges (ACWE) and has become a popular example of energy minimization for image segmentation. However, in their initial formulations, both methods approximate images by piecewise-constant functions, that is, objects are assumed to have a constant intensity. When objects are noisy, or their intensity changes gradually, a piecewise-smooth approximation is better suited, and thus an extension to piecewise-smooth functions was developed (Chan et al., 2007).

When both boundary- and region-derived statistics are not enough, shape-based terms are used. Shape terms provide resilience to false boundaries by heavily penalizing the implausible shape configurations that the false boundaries imply. The most basic terms attempt to achieve boundary smoothness by minimizing curve length, segmentation area, or curvature. More advanced terms compare the shape of the segmentation to some prior model of the shape in an effort to minimize their dissimilarity (Cootes et al., 1992, 1995, 2001; Cootes and Taylor, 1997; Cremers et al., 2001, 2002, 2008; Dambreville et al., 2006; Etyngier et al., 2007; Leventon et al., 2000; Paragios et al., 2006; Pohl et al., 2007; Vu and Manjunath, 2008; Warfield et al., 2000) (see Section 23.1.4 for discussions).

There has even been work trying to combine edge terms, piecewise-constant terms, and shape terms into a single formulation (Bresson et al., 2006). However, with so many competing assumptions about the object and the image inherent in each formulation, some level of trade-off must be established in the resulting functional (i.e., the weights, $\mathbf{w}$, must be set).

If not appropriately set, the weights $\mathbf{w}$ can cause significant error. In fact, our results demonstrated that optimizing the weights has dramatic effects, reducing error in large data sets by as much as 60% (McIntosh and Hamarneh, 2007). However, optimizing the weights by hand for even a single image can be a long and tedious task, with no real guarantee of obtaining the correct segmentation. As such, there has been a number of works that seek to automatically set the weights (Anguelov et al., 2005; Finley and Joachims, 2008; Kolmogorov et al., 2007; McIntosh and Hamarneh, 2007, 2009; Szummer et al., 2008; Taskar et al., 2005 Rao et al., 2009, 2010).

Instead of *guessing* the optimal weights, suppose we write a function $\gamma(\mathbf{w}|I_j, S_j)$ evaluating how well weight $\mathbf{w}$ works for a given image-segmentation pair (I_j, S_j) , such that a parameter is deemed better when it causes S^* to approach S_j , that is, the minimum of E to be the correct segmentation. Given S_j , we could then calculate the ideal weights for a particular image I_j by solving $\mathbf{w}^* = \arg \min_{\mathbf{w}} \gamma(\mathbf{w}|I_j, S_j)$. It is important that γ itself be convex or globally solvable in $\mathbf{w}$. If γ was not globally solvable, uncertainty would remain in that another $\mathbf{w}^*$ may better minimize γ and thus better

segment the image. Similarly, γ cannot contain free parameters, else those parameters would themselves introduce uncertainty, as was the case in McIntosh and Hamarneh (2007).

Recent advances in maximum margin estimation allow for weight optimization wherein the parameters of the objective function are sought such that the highest scoring structures (in our case segmentations) are as close as possible to the ground truth (Anguelov et al., 2005; Finley and Joachims, 2008; Szummer et al., 2008; Taskar et al., 2005). These methods do however assume that a single set of weights works for the entire test set of images, whereas different images can easily require different weights. In contrast, Kolmogorov et al. seek an optimal parameter on a per-image basis. Given a parameter range, their method simultaneously solves the objective function for a set of parameters that bound how the parameters influence the solution (Kolmogorov et al., 2007). Each solution is then treated as a potential segmentation. They propose a number of heuristics, including user intervention, to select the best segmentation from a set of potential ones.

A related topic is that of multiobjective optimization, where methods try to jointly minimize the terms, without weighting them. As the topic relates more to minimizing energy functionals, we defer its discussion until Section 23.1.5.

23.1.2 Segmentation Representation

As expected, all functions must have domains and so in turn energy functionals must have domains. That domain is the space of possible segmentations of the image or shapes. There are many different ways to represent the underlying segmentation, and that choice in turn impacts the image and shape terms that can be readily evaluated. For example, a shape using closed contours pairs most readily with region statistics. Here we summarize some of the most prevalent shape representations in use.

Naturally, we start with the representation originally detailed by Terzopoulos et al., namely the explicit contour model (Kass et al., 1987; Terzopoulos, 1987). The contour is defined as an explicit, parameterized function of its arc length. Integrating along the arc-length integrates along the contour and allows for the evaluation of both internal and external terms (see Appendix B for details). These methods were extended to represent not only contours but surfaces and volumes (Cohen et al., 1992; Cohen and Cohen, 1993; Delingette et al. 1992; McInerney and Terzopoulos, 1995a; Miller et al., 1991; Staib and Duncan, 1992b; Whitaker, 1994). Other explicit models were introduced relating to spring-mass systems, where each boundary point is a mass, connected to other masses via springs (McInerney and Terzopoulos, 1996; Montagnat et al., 2001). There can be other types of masses, namely, internal nodes and medial nodes (Pizer et al., 2003). However, in general these aforementioned works are constrained to a fixed topology, which posed problems in many applications.

There have been two major directions of work to address topological adaptability. The first direction focused on novel ways to automatically re-parameterize the contour or surface enabling the evolution into complex geometries (McInerney and Terzopoulos, 1995b,c, 1999, 2000). Initially developed in 2D, *T-snakes* work by subdividing the image domain into a Freudenthal triangulation (McInerney and Terzopoulos, 1995b,c). At each deformation step, the intersections of the contours with the triangular grids are found, and a set of rules is followed to determine if the contour point should be split or merged. This work was later extended to 3D, with the introduction of *T-surfaces* (McInerney and Terzopoulos, 1999, 2000). Delingette simultaneously developed a somewhat related approach where simplex meshes are used to model the shape, and topological changes are performed “semi-automatically with an automatic detection of topological problems, but a manual validation of all operations” (Delingette, 1999). However, in both cases the explicit re-parameterization of the contour or surface can be costly and may not generalize well to even higher dimensions.

In contrast, implicit contours were built from the ground up to handle changes in topology (Caselles et al., 1997; Osher and Paragios, 2003; Osher and Sethian, 1988; Sethian, 1996). In these representations, the boundary is implied by a given function, instead of explicitly defined. Implicit representations are built around the signed distance function (SDF), where the object boundary is defined as the zero level set of the function. Integrating over the domain of the SDF implicitly integrates over the contour and thus allows for the evaluation of both internal and external terms, as before. Changes in topology are handled internally by the shape representation and require no re-parameterization of the model (Figure 23.4). Similarly, other functions can be used to implicitly represent shapes including characteristic functions (Tsai et al., 2004) and probability maps (Cremers et al., 2008).

More recently, graph methods have emerged where the segmentation is represented by the assignment of labels to a graph (Barrett and Mortensen, 1997; Boykov and Funka-Lea, 2006; Boykov and Jolly, 2001; Boykov and Kolmogorov, 2003; Falcão et al., 1998; Falcão and Udupa, 1997; Grady, 2006; Mortensen and Barrett, 1998; Shi and Malik, 2000). Pixels are represented as vertices in the graphs, and edges between pixel-vertices represent a connectivity neighborhood. Energy functionals, often called cost functions in graph-based works, are expressed as sums over the vertices and their neighborhoods that vary as a function of how each vertex is labeled.

Finally, our discussion thus far has been limited to that of a single object class, but it is also possible to represent multiple object classes at one time, using so-called multi-class shape representations that are built on both implicit (Paragios and Deriche, 2000, 2002; Samson et al., 2000; Vese and Chan, 2001; Zhao et al., 1996) and graph-based representations (Boykov and Jolly, 2001; Grady and Funka-Lea, 2004). Implicit shape models are adapted to multiple classes by defining multiple implicit functions, where the combinations and intersections of the functions denote which class is being represented.

FIGURE 23.4

An exemplar SDF as a shape representation. (a) An SDF undergoing a simple deformation from left to right. (b) The zero level sets of the SDFs, displaying the segmentation each SDF represents. Notice how the topology automatically changes without any re-parameterization. (Reprinted from McIntosh, C., *Energy functionals for medical image segmentation: Choices and consequences*, PhD dissertation, Simon Fraser University, Burnaby, BC, Canada, Copyright 2011. With permission.)

Graph methods, however, are extended by increasing the number of possible labels for each vertex.

In the end, the choice of representation is ultimately determined by the desired segmentation task. As such, it is worth noting that specialized models can exist, where a shape representation is designed specifically for one type of anatomy. A popular example is that of tubular-branching objects, namely, vessels, where cylindrical models can be built and deformed (McIntosh and Hamarneh, 2006; O'Donnell et al., 1994).

23.1.3 Image Representation

As might be expected, how the image is represented will impact how the terms of the energy functional can be evaluated on it. In fact, early on there were many contributions demonstrating how existing techniques could be modified to fit higher dimensional data, vector-valued data (Ballerini, 2001; Chan et al., 2000; Sapiro, 1996; Shah, 1996; Shi et al., 2008), tensor data (Nand et al., 2011; Rousson et al., 2004; Wang and Vemuri, 2004; Weldeselassie and Hamarneh, 2007) (Chapter 19), texture-heavy images (Paragios and Deriche, 2000, 2002), or

even temporal data (Saad et al., 2008; Hamarneh et al., 2004; Tang et al., 2012; Rana et al., 2009; Ng et al., 2012), as opposed to the static, 2D, grayscale images early algorithms were presented on. Furthermore, numerous methods have been adapted to handle the intricacies of specific medical imaging modalities including magnetic resonance images and ultrasound. As an example, we talk briefly about some of the issues inherent to angiography in Section 23.2.

23.1.4 Training Data

A substantial amount of knowledge is often available about anatomical structures of interest—characteristic shape, position, orientation, symmetry, relationship to neighboring structures, associated landmarks, etc. and about plausible image intensity characteristics, subject to natural biological variability or the presence of pathology. Once collected, the training data typically come into the energy functional in the place of shape priors (Cootes et al., 1995), but appearance priors (Cootes et al., 2001) have also been developed (see Heimann and Meinzer (2009) for a complete survey). As shape priors have been a particular area of interest in the field, here we discuss some of the key works.

In many applications, prior knowledge about object shape variability is available or can be obtained by studying a training set of shape examples. This knowledge restricts the space of allowable deformations to a learned shape space that approximates the space of anatomically feasible shapes (Cootes and Taylor, 1997; Cootes et al., 1992, 1995, 2001; Cremers et al., 2001, 2002, 2008; Dambreville et al., 2006; Etyngier et al., 2007; Leventon et al., 2000; Paragios et al., 2006; Pohl et al., 2007; Vu and Manjunath, 2008; Warfield et al., 2000). One of the most notable works in this area is that of Cootes et al., where they introduced and refined active shape models (ASM) (Cootes et al., 1992, 1993, 1995). In ASM, principal component analysis (PCA) is calculated over a set of landmark points extracted from training shapes. The resulting principal components are used to construct a point distribution model (PDM) and an allowable shape domain (ASD). In a natural extension to their previous work, Cootes et al. modify their method to include image intensity statistics (Cootes et al., 2001). Staib and Duncan constrained the deformable models in Fourier space by conforming to probability distributions of the parameters of an elliptic Fourier decomposition of the boundary (Staib and Duncan, 1992a). Statistical prior shape knowledge was also incorporated in implicit, level set-based deformable models. Leventon et al. introduced statistical shape priors by using PCA to capture the main modes of variation of the level set representation (Leventon et al., 2000). However, as Pohl et al. point out, level sets do not form a vector space and hence more accurate shape statistics could be captured by transforming the shapes into a vector space using the logarithm of odds before performing PCA (Pohl et al., 2007).

Though simpler to optimize than their nonlinear counterparts, linear models of shape deformation may not always adequately represent the variance

observed in real data. Linear shape models assume the data lies on a linear manifold, but shapes often lie on nonlinear manifolds where the manifold's properties are not accurately captured by linear statistics (Fletcher et al., 2004). For example, try fitting an ellipse to an "S"-like shape space. In order to include the entire letter, extraneous white space (nonvalid shapes) must also be included. Nonlinear shape models have been introduced to address this problem (Cootes and Taylor, 1997; Cremers, 2008; Cremers et al., 2001, 2002; Dambreville et al., 2006; Etyngier et al., 2007; Fletcher et al., 2004; Sozou et al., 1995).

However, we argue that the problem with linear statistics, as described earlier, is not necessarily due to the application of a linear model to nonlinear data but rather because of the implicit nature in which the statistics are applied (McIntosh and Hamarneh, 2011). By *implicit* we mean the statistics attempt to model variation in the shape, rather than variation in the parameters governing the deformations themselves. Note that we are not referring to the shape representation being implicit or explicit but instead whether the deformations are implicitly or explicitly studied. Implicit shape statistics result from the majority of previous deformable model approaches adopting a boundary-based shape representation, aside from a few exceptions (Pizer, 2003). As a consequence, the statistics are calculated using boundary models of the shape instead of models representing the interior and skeletal topology of the structures. Studying the underlying structural changes of a shape allows deformations that were previously non-convex to be decomposed into linear models. We refer to these as *explicit* shape statistics since they are calculated over the very parameters responsible for varying the object's shape. Consider an object represented by a single pixel. Different images of the object show the pixel moving around in a circle. A nonlinear function is required to describe the pixel's motion and hence no linear statistics can capture the motion adequately as long as it is the object's x, y position being studied. However, once decomposed into a function of $\sin$ and $\cos$, the underlying parameter that controls the objects variability is linear in its variation, and hence linear statistics will yield greatly improved shape statistics. The same argument carries forward, albeit more complexly, to a more complex object. A simple bending of a shape's medial axis is a linear deformation under the appropriate representation, as it is simply a rotation of some of the medial nodes. However, the bending is a highly non-convex deformation once embedded in the image domain, as either an implicit shape (Pohl et al., 2007) or an explicit boundary-based model (Cootes et al., 1995).

23.1.5 Minimizer

Once the image and shape representations have been set and the problem formulated, all that is left is to solve the minimization process and obtain the resulting segmentation. Though it may sound simple enough, this area has been a major focus of criticism of energy minimization-based methods over

the years, and as such has recently become one of the most focused areas for research. Specifically, in their original inception, many of the aforementioned methods were plagued by problems of local minima and sensitivity to initialization. Here we describe the changes and revelations in the field on this topic over the past decade. For a broader review, the interested reader is referred to the following representative, but far from comprehensive, list: Cremers et al., 2011; Grady and Polimeni, 2010; Kolmogorov and Zabini, 2004; and Nikolova et al., 2006.

Energy functional minimization can be carried out in a variety of ways. One solution is to perform explicit differentiation under the Euler–Lagrange equations, where each new application with a modified energy functional must be accompanied by one such derivation (Caselles et al., 1997; Chan and Vese, 2001; Kass et al., 1987; Terzopoulos, 1987) (see Appendix A for details). The result is a set of equations, which, if satisfied, guarantee a stationary point of the energy functional. The solution is then obtained through a gradient-descent process where the change in the shape model (with respect to an artificial time variable) is equated to the Euler–Lagrange equation, that is, the deformable models come to rest when the equations are satisfied (Kass et al., 1987; Terzopoulos, 1987). There are, however, two main drawbacks with this approach. Firstly, performing gradient descent in the presence of image noise can lead to instability in the deformations over time (Sundaramoorthi et al., 2007). Secondly, as the number of dependent variables (shape, location, scale, orientation, etc.) increases so does the complexity of the search space, which often increases the number of local minima and requires the calculation of an increasingly large number of derivatives.

On the issue of stability, there has been work by Sundaramoorthi et al. on reformulating the gradient flow using Sobolev-type inner products, which induce favorable regularity properties into the flow, thus bringing smoother deformations over time (Sundaramoorthi et al., 2007). Recently Bar and Sapiro introduced a Newton-type method built on more generalized norms than the L^2 norm, obtained by equating the Euler–Lagrange constraint to an artificial time variable (Bar and Sapiro, 2009). They include the Sobolev norm and demonstrate improved results over L^2 norms, with faster convergence and more accuracy in the presence of noise. Unless used on convex problems, however, these methods are still prone to local minima.

If local minima do not suffice, global minima must be sought, and as such there have been a number of recent approaches to obtaining the global optima of energy functionals (Andrews et al., 2011b; Appleton and Talbot, 2006; Barrett and Mortensen, 1997; Boykov and Funka-Lea, 2006; Boykov and Kolmogorov, 2003; Bresson et al., 2007; Cremers et al., 2008; Falcão and Udupa, 1997; Falcão et al., 1998; Grady, 2006; Li and Yezzi, 2006; Mortensen and Barrett, 1998; Nikolova et al., 2006). There are three primary directions toward this goal: min-paths, min-cuts, and convex approximations.

Min-path techniques are formulated on the basis of Dijkstra’s algorithm for finding the shortest path in an undirected graph with nonnegative edge weights. They were first presented for 2D interactive segmentation (Barrett

and Mortensen, 1997; Falcão and Udupa, 1997), extended to 3D (Falcão and Udupa, 1997), and later specialized to 4D for vessel segmentation (Li and Yezzi, 2006; Poon et al., 2008, Kawahara et al., 2013, Wink et al., 2004) and 6D (or higher) for spinal cord segmentation (Kawahara et al., 2013).

Graph cuts were demonstrated as a global minimization technique for a popular energy functional (Caselles et al., 1997), as a special case of computing a geodesic on a Riemannian space whose metric is computed from the image (Boykov and Kolmogorov, 2003). However, graph cuts have been shown to apply only to a restricted class of energy functionals that are submodular (Kolmogorov and Zabini, 2004), and their solutions are discrete approximations to the continuous formulations whose accuracy is dependent on the resolution of the approximating graph (Boykov and Kolmogorov, 2003). Naturally, as that resolution increases so does their running time. Random walkers were developed in a similar nature, solving image segmentation as a graph problem wherein the global optimum is obtained to a particular cost function (Grady, 2006). In fact, graph cuts and random walkers have been shown to be specific instantiations of a single framework (Sinop and Grady, 2007).

Another line of work has come from the relaxation of the underlying shape model from a non-convex space to a convex one, thereby defining convex energy functionals that can then be minimized instead of their non-convex counterparts. This convex relaxation work, which began in 2004 with a simple restricted class of functionals (Nikolova et al., 2006), was later extended to a broader class in Bresson et al. (2007), and then a similar work appeared in 2008 with the addition of a shape prior (Cremers et al., 2008). However, restrictions still exist in that the functionals and the shape spaces they are optimized over must be convex when defined over the relaxed space and that the relaxed shape space must itself be convex.

Though not guaranteed to find global optima, genetic algorithms (GAs) have also been applied to the minimization of energy functionals (Ballerini, 1998, 2001; Fan et al., 2002; Ibáñez et al., 2009; MacEachern and Manku, 1998; McIntosh and Hamarneh, 2011; Tohka, 2001). At a high level, GAs work by performing many simultaneous local searches, each individually optimizing the energy functional via a random walk in the search space. At the end of the process, the search that yielded the lowest value for the energy functional is adopted as the segmentation.

Ballerini extends the classical active contour models, developed by Terzopoulos (1987), by using GA to directly minimize the standard energy functional (Ballerini, 1998). Members of the GA population are hypothetical shape configurations, represented by their explicit contour locations. The method was later extended to color images by using one image term per color channel (Ballerini, 2001). MacEachern and Manku presented a similar method using a binary representation of the contour (MacEachern and Manku, 1998). Similarly, Tohka presented simplex meshes paired with image-based energies, minimized via a hybrid GA-greedy approach, and applied

the technique to the segmentation of 3D medical images (Tohka, 2001). Fan et al. also developed a GA method for an explicit active contour but describe their method using Fourier descriptors and employ parallel GAs to speed up minimization (Fan et al., 2002). A different shape representation, known as topological active nets, is used by Ibáñez et al. to enable the segmentation of objects with unknown topologies or even multiple objects in the same scene (Ibáñez et al., 2009). However, aside from simple boundary smoothness constraints, all of these methods are based on classical active contour models or their variants without incorporating prior shape knowledge, making them prone to latching to erroneous edges and ill-equipped to handle gaps in object boundaries (as was discussed in Section 23.1.1).

In Hill and Taylor (1992), GAs were used with statistically based ASMs, where the parameter space consists of possible ranges of values for the pose and shape parameters of the model. The objective function to be maximized reflects the similarity between the gray levels related to the object in the search stage and those found from training. Additional works use convex, implicit, global shape statistics assuming a Gaussian distribution around a mean shape (Ghosh and Mitchell, 2006; Mignotte and Meunier, 1999; Ruff et al., 1999). Mignotte and Meunier (1999) incorporate prior shape information by defining the mean as a circular deformable template, while Ruff et al. (1999) use a PDM for occluded shape reconstruction, and Ghosh and Mitchell (2006) use a level set shape representation and a learned mean from training data. Although these techniques apply GAs to produce generations of plausible populations of shapes, the statistically based deformations are convex and may not offer the required flexibility to accommodate for non-linear shape deformations. In McIntosh and Hamarneh (2011), we address this problem by using GAs to optimize statically based deformations that explicitly study the underlying shape variations, thus reducing the problem with linear shape statistics described in Section 23.1.4.

A somewhat related direction is that of multiobjective optimization, where each term is simultaneously optimized rather than optimizing a linear sum of the terms (23.1). Hence, in multiobjective optimization no weights are provided to combine the competing terms of the functional, instead a solution is sought for which no term can be improved without sacrificing another (Collette and Siarry, 2002). That solution is known as a *Pareto optimal* solution (Collette and Siarry, 2002). The set of Pareto optimal solutions for a given problem is known as the *Pareto front*, and there is no preference among them unless a ranking is provided between the objectives. Nakib et al. recently used multiobjective optimization to determine the parameters for a thresholding algorithm for image segmentation (Nakib et al., 2010). Hanning et al. present an approach using a piecewise approximation of the image similar to the Mumford-Shah model (Mumford and Shah, 1989) using multiobjective optimization to decide the trade-off between the number of segments and the image approximation error (Hanning et al., 2006). It is interesting to note that, for convex functions, if the ground truth lies on the Pareto front, then by definition a set of weights

must exist that causes the optima to be the ground truth for the linear sum of terms formulation (23.1) (Geoffrion, 1968). In other words, a linear sum of terms model exists that yields the same segmentation as the multiobjective model, which is far more challenging to optimize. However, the necessary weights needed to achieve the desired segmentation are unknown. Weight optimization attempts to determine these weights (Section 23.1.1).

23.1.6 Related Methods

Though our discussion thus far has been focused on energy minimization methods for image segmentation that follow the prescribed building blocks, there are a few bodies of related research that follow a different path. Here we briefly detail two of them.

23.1.6.1 Relation to Bayesian Methods

Throughout this chapter, we have examined numerous methods built on energy functionals of the form $E(S|I, \mathbf{w}) = w_1 \times \text{internal}(S) + w_2 \times \text{external}(S, I)$. However, an interesting parallel to probabilistic approaches can be observed with a few simple assumptions and manipulations of this general form. Here we demonstrate that this model is actually equivalent to performing image segmentation via Bayesian inference. First, we restate the segmentation problem as

$$S^* = \arg \max_S P(S | I, \mathbf{w}), \quad (23.3)$$

where

$$P(S | I, \mathbf{w}) = \frac{P(I | S, \mathbf{w}) P(S | \mathbf{w})}{P(I | \mathbf{w})}. \quad (23.4)$$

Maximizing (23.3) is equivalent to minimizing its negative logarithm

$$S^* = \arg \min_S (-\log P(S | I, \mathbf{w})), \quad (23.5)$$

where $-\log P(I | S, \mathbf{w}) - \log P(S | \mathbf{w})$, and the denominator has been removed as it has no consequence on the minimization. Now suppose we model our probabilities as

$$\begin{aligned} P(S | \mathbf{w}) &= e^{-w_1 \times \text{internal}(S)} \\ P(S | I, \mathbf{w}) &= e^{-w_2 \times \text{external}(S, I)} \end{aligned} \quad (23.6)$$

then substituting back into (23.5) yields

$$S^* = \arg \min_S (-\log P(S | I, \mathbf{w})) = w_1 \times \text{internal}(S) + w_2 \times \text{external}(S, I), \quad (23.7)$$

as before. From here it becomes possible to examine many of the approaches previously cited and see what independence assumptions they are making from a Bayesian standpoint.

23.1.6.2 Relation to Segmentation via Registration

Thus far we have discussed methods where the dependent function of the energy functional is one describing the shape of the current segmentation. However, a related field exists where the dependent function is instead a spatial transformation describing how one or more images are related. This is the field known as image registration, and it involves finding a mapping from the spatial coordinates of one image to another, identifying which pixels in a source image map to which pixels in a target image. Image registration can be used for segmentation when the mapping from a novel image is found to a training image with a known segmentation, since that mapping effectively labels the novel image. As this field is far too large and diverse to cover here, we refer the interested reader to Maintz and Viergever (1998), Zitová and Flusser (2003), and Chapter 22, for a complete survey. We do note, however, that many of the same issues discussed in this chapter, that is, global versus local optima and setting the weights for the energy functional, are also important problems in registration.

23.2 MIS via Energy Minimization

As already noted in this chapter, energy minimization methods have been applied to a wide variety of MIS problems. Two popular application domains are those of cardiac images and vascular images. As an example of how energy minimization can be applied to MIS, here we briefly discuss some key works relating to vascular segmentation. Though a complete survey of energy minimization for MIS does not exist, the interested reader is referred to McNerney and Terzopoulos (1996) for a related survey of MIS using deformable models.

One structure of particular interest in the diagnosis and understanding of many diseases is vasculature (Bullitt et al., 2003). Vessel segmentation remains an interesting application area of energy minimization methods because of its unique challenges. Firstly, the topology is complex, and as such many of the already mentioned topology-adaptive shape models were first demonstrated in their application to vessel segmentation (McNerney and Terzopoulos, 2000). Secondly, the vessels are often of very low contrast motivating advances in image terms (Frangi et al., 1999; Vasilevskiy and Siddiqi, 2002; Wink et al., 2001, 2004). For example, Vasilevskiy and Siddiqi built flux-maximizing geometric

flows based on the observation that the gradient vector field near a vessel should be orthogonal to the vessel (Vasilevskiy and Siddiqi, 2002). They define a flux-maximizing geometric flow as one for which the inward normals of the underlying curve align with the direction of the gradient vector field. Near vessels the gradient vector field points inward toward the vessel centerline, and thus maximizing the flux will align the boundary of the segmentation to the boundary of the vessel. The last major challenge in vessel segmentation is that the vessels can be very thin, pushing the boundaries of numerical stability in many techniques and motivating new methods with increased stability to thin structures (Lorigo et al., 2001; Sundaramoorthi et al., 2007). For example, Lorigo et al. modify GAC to deform along the medial axis of a tubular shape, as opposed to its surface (Lorigo et al., 2001). For a complete survey of vessel segmentation techniques, the reader is referred to Lesage et al. (2009).

23.3 Discussion

Having briefly touched on each of the five primary building blocks of energy minimization methods, we conclude with a discussion of the main issues concerning their usage for MIS, namely, issues relating to how to build the energy functional, represent the segmentation, deal with the different imaging modalities themselves, train priors, and finally minimize the resulting system. We begin by touching briefly on issues relating to validating the method, as that is a fundamental step that we have not yet discussed.

Every MIS method must be validated. There are two main approaches to validate an MIS method, expert segmentations and synthetic data, each of which has its own inherent advantages and drawbacks. Expert segmentations can be time consuming and costly to obtain. Furthermore, expert segmentations suffer from both inter- and intraoperator variability because multiple experts, or even the same expert on different days, can obtain differing segmentations of the same object. Warfield et al. attempt to address problems with inter- and intraoperator variability through an expectation-maximization algorithm that weights different segmentations according to a variety of measurements and rules (Warfield et al., 2004). The key advantage to expert segmentations of real medical data is that the data is real and hence it demonstrates the applicability of the method to the problem at hand. Synthetic data can be created by either physical or computational phantoms. Physical phantoms are those physically constructed and then imaged in some manner, whereas computational phantoms are simulated using mathematical models designed to replicate human anatomy under specific imaging protocols (Cocosco et al., 1997; Hamarneh and Jassi, 2010). The main drawback in both cases is realism: segmenting a phantom well does not necessarily mean real data will also be segmented with high accuracy. The main advantage of synthetic data is certainty about the ground-truth segmentations. In Hamarneh et al. (2008), a hybrid method based

on synthesizing deformation of a real data is presented. Whether real data or synthetic data, a measure of dissimilarity between the automatic segmentation and the ground truth must eventually be computed. Standard approaches for evaluating segmentation results given ground-truth segmentation include the Hausdorff distance, the Dice similarity coefficient (Dice, 1945), the Jaccard index (Jaccard, 1901), and the Tanimoto coefficient (Tanimoto, 1957).

Choosing the right energy functional for the given task is a crucial first step. Ideally, one hopes for strictly convex functions with their global minima lying at the correct segmentations for a given set of images, but this ideal scenario is rarely the case. The main challenges here are determining what energy terms could make a good functional and how to weight them in a such way as to best segment the images. In other words, one must appreciate the trade-off between the fidelity of the energy functional (how accurately it models the segmentation problems at hand) and its optimizability (how attainable is the functional's global optimum) (Hamarneh et al., 2011; Ulen et al., 2013).

There are often two main concerns when choosing the segmentation representation. Firstly, will it allow for the training of appropriate shape priors? Secondly, will it introduce problems in the minimization stage? Some shape representations do not form vector spaces, and thus performing statistics on them is difficult. Level sets (SDFs) are one such example, where a specific method for computing statistics over the resulting shape space was needed (Pohl et al., 2007). Level set-based representations can also cause problems in the minimization stage, as they do not form a convex space, and thus introduced non-convexity into the minimization problem (Cremers et al., 2008). However, they remain a popular technique due to the sub-pixel accuracy and automatic handling of topological changes. A more recent representation is the isometric log ratio (Changizi and Hamarneh, 2010) that has been used for segmentation of anatomical images (Andrews et al., 2011a,b).

Each imaging modality has its own inherent problem associated with it relating to different types of noise and spatial or temporal resolution of the structure of interest. As already exemplified with a brief treatment of blood vessel segmentation methods, each application can require customized energy functionals, segmentation representations, and optimization strategies.

When training priors, one is often forced to balance two competing goals: having the priors accurate versus having the resulting energy functional solvable. Linear statistics do not often fit the training data well but lead to easily solved energy functionals, whereas nonlinear statistics fit the data but are difficult to work with. The problem with linear statistics, however, is often not necessarily due to the application of a linear model to nonlinear data but rather due to the global aspect of the shape statistics themselves and due to the shape representation to which they are applied. Global shape statistics are those that model the shape variation of the entire shape simultaneously, that is, each shape is a single point in some high-dimensional space and the statistics (linear or not) describe some restricted set of that space. Many deformable model approaches adopt a boundary-based representation.

As a consequence the statistics are calculated using boundary models of the shape instead of models representing the interior and skeletal topology of the structures, leading to a loss of accuracy (McIntosh and Hamarneh, 2011).

The primary problem in minimization remains how to globally optimize an increasingly large set of energy functionals, as opposed to the restricted sets seen thus far (Bresson et al., 2007; Cremers et al., 2008; Kolmogorov and Zabini, 2004). Interestingly enough, even with global minima, existing functionals are not proving accurate enough, motivating the search for new energy terms or ways of building functionals that can better respect the image variability.

In short, developing MIS methods remains a daunting task from start to finish with numerous areas for research relating to each of the five building blocks commonly found in energy minimization techniques. However, with the ever-growing popularity of medical imaging for diagnosis and disease understanding, developing robust and automatic techniques for MIS remains an important goal. In order to reach that goal, we must continue to make breakthroughs in terms of accuracy and reliability of MIS methods. To do that, we need to consider where the bulk of the error and performance variability is coming from, so as to best focus our efforts there.

With fully automatic segmentation remaining an unsolved problem, user-based inspection and delineation of medical images is indispensable. This is trivial for scalar fields, but for complex manifold-valued images, even displaying these images requires careful considerations.

Realizing the challenge in achieving accurate yet fully automatic segmentation methods, recent methods opted to calculate the uncertainty in a resulting segmentation (e.g., via Shannon's entropy of probabilistic segmentation) and utilizing the uncertainty measures in active- and self-learning strategies (Andrews et al., 2011a,b; Changizi and Hamarneh; 2010, Saad et al., 2010a,b; Top et al., 2010, 2011).

Appendix 23.A: Euler–Lagrange

Starting with a function $\Phi(x)$, we build an energy functional

$$E(\Phi) = \int L(x, \Phi(x), \Phi_x(x), \Phi_{xx}(x)) dx \quad (23.A.1)$$

where Φ_x is the first derivative of Φ with respect to x and Φ_{xx} the second. The functional E describes a desirable feature of Φ , in that it takes a high value when Φ is doing poorly and a low value when Φ is doing well. We know from Fermat's theorem that E obtains its extremum at a stationary point, that is, where the derivative is zero. To describe a stationary point one typically writes

$$\lim_{\tau \rightarrow 0} \frac{E(\Phi + \tau\omega) - E(\Phi)}{\tau} = 0 \quad (23.A.2)$$

where ω is a scalar, but here ω is a function, so this equation is known as the *first variation*, as opposed to first derivative, of the functional. Developed in the 1750s, the Euler–Lagrange equation plays a fundamental role in variational calculus, defining a necessary condition under which the first variation tends to zero, and therefore the functional reaches a stationary point (Els golc, 1962). For a functional E as described earlier, the general form of the Euler–Lagrange differential equation is

$$\frac{\partial L}{\partial \Phi} - \frac{\partial}{\partial x} \left(\frac{\partial L}{\partial \Phi_x} \right) + \frac{\partial}{\partial x^2} \left(\frac{\partial L}{\partial \Phi_{xx}} \right) = 0 \quad (23.A.3)$$

See Appendix B for an example of its application to energy minimization methods for MIS.

Appendix 23.B: Snakes: Details and Derivations

Classical deformable shape models (Terzopoulos, 1987) are represented as a 2D parametric contour $\mathbf{v}(s) = (x(s), y(s))$, where $s \in [0,1]$ traverses the contour (Figure 23.B.1) and $\mathbf{v}$ is deformed to fit to image data by minimizing an energy term ξ

$$\xi(\mathbf{v}(s)) = \alpha(\mathbf{v}(s)) + \beta(\mathbf{v}(s)), \quad (23.B.1)$$

which depends on both the shape of the contour and the image data $I(x,y)$ reflected via the internal and external energy terms, $\alpha(\mathbf{v}(s))$ and $\beta(\mathbf{v}(s))$, respectively.

The internal energy term is given as

$$\alpha(\mathbf{v}(s)) = \int_0^1 \frac{1}{2} (w_1 \|\mathbf{v}_s\|^2 + w_2 \|\mathbf{v}_{ss}\|^2) ds, \quad (23.B.2)$$

FIGURE 23.B.1

A parameterized contour undergoing a simple deformation (left to right). (Reprinted from McIntosh, C., Energy functionals for medical image segmentation: Choices and consequences, PhD dissertation, Simon Fraser University, Burnaby, BC, Canada, Copyright 2011. With permission.)

whereas the external energy term is given as

$$\beta(\mathbf{v}(s)) = \int_0^1 w_3(s) P(\mathbf{v}(s)) ds. \quad (23.B.3)$$

The weighting functions w_1 and w_2 control the tension and flexibility of the contour, respectively, and w_3 controls the influence of image data. w_i 's can depend on s but are typically set to different constants. For the contour to be attracted to image features, the function $P(\mathbf{v}(s))$ is designed such that it has minima where the features have maxima. For example, for the contour to be attracted to high-intensity changes (high gradients), we can choose

$$P(\mathbf{v}(s)) = P(x(s), y(s)) = -\|\nabla [G_\sigma * I(x(s), y(s))]\| \quad (23.B.4)$$

where $G_\sigma * I$ denotes the image convolved with a smoothing (e.g., Gaussian) filter with a parameter σ controlling the extent of the smoothing (e.g., variance of Gaussian).

The contour $\mathbf{v}$ that minimizes the energy ξ must, according to the calculus of variations (Elsgolc, 1962), satisfy the vector-valued partial differential (Euler–Lagrange) equation

$$\frac{\partial f}{\partial \mathbf{v}} - \frac{\partial}{\partial s} \left(\frac{\partial f}{\partial \mathbf{v}_s} \right) + \frac{\partial^2}{\partial s^2} \left(\frac{\partial f}{\partial \mathbf{v}_{ss}} \right) = 0 \quad (23.B.5)$$

where $f = \frac{1}{2} (w_1 \|\mathbf{v}_s\|^2 + w_2 \|\mathbf{v}_{ss}\|^2) - w_3 \|\nabla(G_\sigma * I(\mathbf{v}))\|$. The first step in applying the Euler–Lagrange is to determine the partial derivatives as follows:

$$\begin{aligned} \frac{\partial f}{\partial \mathbf{v}} &= -w_3 \nabla \|\nabla(G_\sigma * I(\mathbf{v}))\| \\ \frac{\partial}{\partial s} \left(\frac{\partial f}{\partial \mathbf{v}_s} \right) &= w_1 \mathbf{v}_{ss} \\ \frac{\partial^2}{\partial s^2} \left(\frac{\partial f}{\partial \mathbf{v}_{ss}} \right) &= w_2 \mathbf{v}_{ssss} \end{aligned} \quad (23.B.6)$$

Then substituting back into Equation 23.B.5, we get the final set of equations

$$-w_1 \mathbf{v}_{ss} + w_2 \mathbf{v}_{ssss} - w_3 \nabla \|\nabla(G_\sigma * I)\| = 0 \quad (23.B.7)$$

where we make note that $\mathbf{v}(s) = (x(s), y(s))$, and so the earlier equation can be expanded to

$$\begin{aligned} -w_1 x_{ss} + w_2 x_{ssss} - w_3 \frac{\partial \|\nabla(G_\sigma * I)\|}{\partial x} &= 0 \\ -w_1 y_{ss} + w_2 y_{ssss} - w_3 \frac{\partial \|\nabla(G_\sigma * I)\|}{\partial y} &= 0 \end{aligned} \quad (23.B.8)$$

In order to solve the system of equations, we introduce an artificial time step, by equating the earlier equations to $-\partial \mathbf{v} / \partial t$. This yields a first-order iterative optimization method, though as outlined in this report other choices for optimization methods exist.

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