Incorporating prior knowledge in medical image segmentation: a survey

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Abstract

Medical image segmentation, the task of partitioning an image into meaningful parts, is an important step toward automating medical image analysis and is at the crux of a variety of medical imaging applications, such as computer aided diagnosis, therapy planning and delivery, and computer aided interventions. However, the existence of noise, low contrast and objects’ complexity in medical images are critical obstacles that stand in the way of achieving an ideal segmentation system. Incorporating prior knowledge into image segmentation algorithms has proven useful for obtaining more accurate and plausible results. This paper surveys the different types of prior knowledge that have been utilized in different segmentation frameworks. We focus our survey on optimization-based methods that incorporate prior information into their frameworks. We review and compare these methods in terms of the types of prior employed, the domain of formulation (continuous vs. discrete), and the optimization techniques (global vs. local). We also created an interactive online database of existing works and categorized them based on the type of prior knowledge they use. Our website is interactive so that researchers can contribute to keep the database up to date. We conclude the survey by discussing different aspects of designing an energy functional for image segmentation, open problems, and future perspectives.

Keywords: Prior knowledge, targeted object segmentation, review, survey, medical image segmentation

1. Introduction

Image segmentation is the process of partitioning an image into smaller meaningful regions based in part on some homogeneity characteristics. The goal of segmentation is to delineate (extract or contour) targeted objects for further analysis. For example, in medical image analysis (MIA), image segmentation of organs or tissue types is a necessary first step for numerous applications, e.g. measuring tumour burden (or volume) from positron emission tomography (PET) or computed tomography (CT) scans (Hatt et al., 2009; Bagci et al., 2013), analyzing vasculature from magnetic resonance angiography (MRA) (e.g. measuring tortuosity) (Bullitt et al., 2003; Yan and Kassim, 2006), grading cancer from histopathology images (Tabesh et al., 2007), performing fetal measurements from prenatal ultrasound (Carneiro et al., 2008), performing augmented reality in robotic image guided surgery (Su et al., 2009; Pratt et al., 2012), building statistical atlas for population studies and voxel-based morphometry (Ashburner and Friston, 2000).

Given an input image, I, the goal of a typical image segmentation system is to assign every pixel in I a specific label where each label represents a structure of interest. Several traditional segmentation algorithms have been proposed for assigning labels to pixels; these include thresholding (Otsu, 1975; Sahoo et al., 1988), region-growing (Adams and Bischof, 1994; Pohle and Toennies, 2001; Pan and Lu, 2007), watershed (Vincent and Soille, 1991; Grau et al., 2004; Hamarneh and Li, 2009) and optimization-based methods (Grady, 2012; McIntosh and Hamarneh, 2013a; Ulén et al., 2013). The existence of noise, low contrast and objects’ complexity in medical images, typically cause the aforementioned methods to fail. In addition, all these traditional methods assume that objects’ entire appearance have some notion of homogeneity; however, this is not necessarily the case for complex objects (e.g. multi-region cells with membrane, nucleus and nucleolus; or brain regions affected by magnetic field of a magnetic resonance imaging (MRI) device non-uniformity). Many real-world objects are better described by a combination of regions with distinct appearance models. This is where more elaborate prior information about the targeted objects becomes helpful.

The majority of state-of-the-art image segmentation methods are formulated as optimization problems, i.e. energy minimization or maximum-a-posteriori estimation, mainly because of their: 1) formal and rigorous mathematical formulation, 2) availability of mathematical tools for optimization, 3) capability to incorporate multiple (competing) criteria as terms in the objective function, 4) ability to quantitatively measure the extent by which a method satisfies the different criteria/terms, and 5) ability to examine the relative performance of different solutions.

In this paper, we review the various types of prior information that are utilized in different optimization-based frameworks for segmentation of targeted objects. Prior information can take many forms: user interaction; appearance models; boundaries and edge polarity; shape models; topology specification; moments (e.g. area/volume and centroid constraints); geometrical...
interaction and distance prior between different regions/labels; and atlas or pre-known models. We compare the different methods utilizing prior information in image segmentation in terms of the type of prior information utilized, domain of formulation (continuous vs. discrete) and optimization techniques (global vs. local) used.

The rest of the paper is organized as follows. In Section 2, we briefly review the previous surveys that covered the medical image segmentation (MIS) problems and justify the need for our survey. In Section 3, we review the fundamentals of optimization-based image segmentation techniques. In Section 4, we give a concrete overview of the different types of prior knowledge devised to improve image segmentation. Finally, in Section 5, we summarize our notes and elaborate on future perspectives.

2. Why yet another survey paper on MIS?

Many survey papers on the topic of medical image segmentation have appeared before and in this section, we explore the related surveys.

McInerney and Terzopoulos (1996) reviewed the development and application of deformable models to problems in medical image analysis, including segmentation, shape representation, matching and motion tracking. Pham et al. (2000) surveyed some of the segmentation approaches such as thresholding, region growing and deformable models with an emphasis on the advantages and disadvantages of these methods for medical imaging applications. Olabbarriaga and Smeulders (2001) presented a review of the user interaction in image segmentation. In Olabbarriaga and Smeulders (2001), the goal was to identify patterns in the use of user-interaction and to propose a criteria to evaluate interactive segmentation techniques. All of these surveys are limited to specific segmentation techniques that adopted a few basic priors such as intensity and texture. In addition, the aforementioned surveys (McInerney and Terzopoulos, 1996; Pham et al., 2000; Olabbarriaga and Smeulders, 2001) are more than 10 years old and many important new developments have appeared since then.

Elnakib et al. (2011) and Hu et al. (2009) focus on appearance and shape features and overview most popular medical image segmentation techniques such as deformable models and atlas-based segmentation techniques. Heimann and Meinzer (2009) reviewed several statistical shape modelling approaches. Shape representation, shape correspondence, model construction, local appearance model, and search algorithms structured their survey. Peng et al. (2013) present five categories of graph-based discrete optimization strategies to MIS within a graph-theoretical perspective and hence do not discuss specific forms of priors the way we do in this survey. McIntosh and Hamarneh (2013b) surveyed the field of energy minimization in MIS and provided an overview on the energy function, the segmentation and image representation, the training data, and the minimizers. Many advanced prior information proposed in recent years have not been included in the aforementioned surveys.

Some surveys are focused on specific modalities only. As an example, Noble and Boukerroui (2006) focused on reviewing methods on ultrasound segmentation in different medical applications, including cardiology, breast, and prostate. In Sharma and Aggarwal (2010), the details of automated segmentation methods, specifically in the context of CT and MR images, were discussed. All the method discussed in this survey adopted limited forms of priors such as appearance, edge, and shape.

Other surveys focused on specific organs. For example, Lesage et al. (2009) reviewed literature on 3D vessel lumen segmentation while Petitjean and Dacher (2011) reviewed fully and semi-automated methods performing segmentation in short axis images of cardiac cine MRI sequences. They propose a categorization for cardiac segmentation methods based on what level of external information (prior knowledge) is required and how it is used to constrain segmentation. However, the discussed priors in Petitjean and Dacher (2011) are limited to shape and appearance information in deformable contour and atlas-based methods.

The recent paper, Grady (2012) is most similar to this survey and includes a solid introduction to targeted object segmentation. However, this survey focused on graph-based methods only and studied only a subset of priors we cover in this report.

In this survey, we categorize several prior information based on their types and discuss how these priors have been encoded into segmentation frameworks both in continuous and discrete settings. The prior information discussed in this survey has been proposed in both computer vision and medical image analysis communities. We hope this survey would be useful for the MIA community and the users of medical image segmentation techniques by: summarizing what types of priors exist so far; which ones can be useful for one’s own targeted segmentation problems; which methods (papers) have incorporated such priors in their formulation already; the approach adopted for incorporating certain priors (the associated complexities and trade-offs). We also hope that by surveying what has been done, researchers can more easily identify existing “gaps” and “weaknesses”, e.g. identifying other important priors that have been missed so far and require future research; or proposing better techniques for incorporating known priors.

3. Fundamentals of image segmentation

3.1. Traditional image segmentation methods

As mentioned in Section 1, several traditional segmentation algorithms have been proposed in the literature including thresholding, region-growing, and watershed.

Thresholding is the simplest segmentation technique where, for a simple case of binary segmentation (foreground vs. background), the input image is divided into regions: regions with values either less or more than a threshold. Determining more than one threshold value is called miltithresholding (Sahoo et al., 1988). In thresholding, segmentation results depend on the image properties and on how the threshold is chosen (e.g. using Otsu’s method (Otsu, 1975)). Thresholding
techniques do not take into account the spatial relationships between features in an image and thus are very sensitive to noise.

Region growing methods start from a set of seed pixels defined by the user and examine neighbouring pixels of the seeds to determine whether the neighbouring pixels should be added to the region preserving some uniformity and connectivity criteria (Adams and Bischof, 1994). Different variations of this technique have been applied on different medical image modalities (Pohle and Toennies, 2001; Pan and Lu, 2007). Region growing methods consider the neighbourhood information of pixels, and hence, they are more robust to noise compared to thresholding methods. However, these methods are sensitive to the chosen “uniformity predicate” (a logical statement for evaluating the membership of a pixel) and corresponding threshold (Adams and Bischof, 1994), the location of seeds, and type of pixel connectivity.

In conventional watershed algorithms (Vincent and Soille, 1991), an image may be seen as a topographic relief, where the intensity value of a pixel is interpreted as its altitude in the relief. Suppose that the entire topography is flooded with water through virtual “holes” at the bottom of basins, then as the water level rises and water from different basins are about to merge, a dam is built to prevent merging. These dam boundaries correspond to the watershed lines or boundaries of basins. An improved version of the watershed technique has been used to segment brain MR images (Grau et al., 2004; Hamarneh and Li, 2009). In practice, watershed produces over-segmentation due to noise or local irregularities in the image. Marker-based watershed (Grau et al., 2004; Vincent, 1993; Beucher, 1994) prevents over-segmentation by limiting the number of regional minima. However, this method is also sensitive to noise.

Having prior knowledge about the objects of interest and incorporating this knowledge into the segmentation framework helps us overcome the shortcomings associated with the traditional methods and obtain more plausible results. As mentioned earlier, formulating image segmentation as an optimization problem allows for the use of multiple criteria and prior information as energy terms in an objective functional. In the following section, we briefly review the fundamentals of optimization-based techniques for medical image segmentation.

3.2. Optimization-based image segmentation

Given an image $I: \Omega \subseteq \mathbb{R}^n \rightarrow \mathbb{R}^m$, image segmentation partitions $\Omega$ into $k$ disjoint regions $S = \{S_1, \ldots, S_k\} \subset S$ such that $\Omega = \bigcup_{i=1}^{k} S_i$, and $S_i \cap S_j = \emptyset, \forall i \neq j$. $S$ is the solution space. The aforementioned partitioning is referred to as a crisp binary (when $k = 2$) or multi-region ($k > 2$) segmentation. In a fuzzy or probabilistic segmentation, each element in $\Omega$ (e.g. a pixel) is assigned a vector $p$ of length $k$ quantifying the memberships or probabilities of belonging to each of the $k$ classes, $p = [p_1, p_2, \ldots, p_k]$ where $p_i \geq 0, i = 1, \ldots, k$ and $\sum_{i=1}^{k} p_i = 1$. This task of image partitioning can be formulated as an energy minimization problem. An energy function, $E: S \rightarrow \mathbb{R}$, usually consists of several objectives that are divided into two main categories: regularization terms, $R_i: S \rightarrow \mathbb{R}$, and data terms, $D_i: S \rightarrow \mathbb{R}$. The regularization terms correspond to priors on the space of feasible solutions and penalize any deviation from the enforced prior such as shape, length, etc. The data terms measure how strongly a pixel should be associated with a specific label/segment. These objectives (regularization and data terms) can then be scalarized as:

$$E(S) = \lambda \sum_i R_i(S) + \sum_i D_i(S; I). \quad (1)$$

The optimization problem is then formulated as:

$$S^* = \arg \min_S E(S) = \arg \min_S \lambda R(S) + D(S; I), \quad (2)$$

where $S^* = \{S_1^*, \ldots, S_k^*\}$ are the optimal solutions and, for simplicity, $R$ and $D$ represent all the regularization and data terms, respectively. $\lambda$ is a constant weight that balances the contribution/importance of the data term and the regularization term in the minimization problem.

One example of such energy is written as:

$$S_1^*, \ldots, S_k^* = \arg \min_{S_1, \ldots, S_k} \left\{ \lambda \sum_{i=1}^{k} \int_{S_i} dx + \sum_{i=1}^{k} \int_{S_i \setminus \partial S_i} D_i(x; I)dx \right\}, \quad (3)$$

where the first term (regularization term) measures the perimeter of the segmented regions $S_i$ and penalizes large perimeters, thus favouring smooth boundaries. $D_i(x): \Omega \rightarrow \mathbb{R}$, associated with region $S_i$, measures how strongly pixel $x \in \Omega$ should be associated with region $S_i$. In Section 4.3, we discuss different types of regularization terms used in image segmentation problems.

An optimization-based image segmentation problem can also be formulated as a maximization problem:

$$S^* = \arg \max_S P(S|I), \quad (4)$$

where $S^*$ is the optimal segmentation. Using Bayes’ theorem, (4) can be written as:

$$S^* = \arg \max_s \frac{P(IS)P(S)}{P(I)} \equiv \arg \max_s P(IS)P(S). \quad (5)$$

In (4) and (5), $P(IS)$ is the posterior probability that defines the degree of belief in $S$ given the evidence $I$ (or some features of $I$), $P(IS)$ is the image likelihood measuring the probability of the evidence in $I$ given the segmentations $S$, and $P(S)$ is the prior probability that indicates the initial (prior to observing $I$) degree of belief in $S$. Maximizing the posterior probability (5) is equivalent to minimizing its negative logarithm:

$$S^* = \arg \min_s - \log P(IS) - \log P(S). \quad (6)$$

The probability (6) and energy (2) notations are related via the Gibbs and Boltzmann distribution. Ignoring the Boltzmann’s constant and thermodynamic temperature (as they do not affect the optimization) and substituting $P(IS) \propto e^{-DK(S,I)}$ and $P(S) \propto e^{-\beta E(S)}$ into (6), we obtain (2).

To avoid terminological confusion, we emphasize that to improve a segmentation, prior knowledge can be incorporated into one or both of the regularization and data terms. Hence, the term prior knowledge itself should not be confused with the prior probability in (5).
3.3. Domain of formulation: continuous vs. discrete

In general, a segmentation problem can be formulated in a spatially discrete or continuous domain. In the community that advocates continuous methods, it is assumed that the world we live in is a continuous world (continuous $\Omega$). However, images captured by digital cameras are discrete both in space and color/intensity. The discretization in space is called sampling (discrete $\Omega$) and the discretization in color/intensity or value space is called quantization. Given this categorization, we have four different cases for image representation (Figure 1).

The energy function describing a segmentation problem can also be formulated in a discrete or continuous domain. Depending on the solution space (discrete vs. continuous) and the energy values, four possible cases can be considered for an energy functional (Figure 2). In the spatially discrete setting, the energy function is defined over a set of finite variables (nodes $\mathcal{P} \subset \Omega$ and edges), leading to the adoption of graphical models (Wang et al., 2013). One of the most commonly used graphical models is the Markov random field (MRF) (Wang et al., 2013). In MRF formulations, solutions are often calculated using graph cut methods, e.g. max-flow/min-cut algorithms or graph partitioning methods. Conversely, in the spatially continuous setting, energy functionals are continuous and so are the optimality conditions, which are written in terms of a set of partial differential equations (PDE). The minimization problem in (3) is a continuous version of a multi-region segmentation functional, often called minimal partition problem in the PDE community (Nieuwenhuis et al., 2013). Note that in Figure 2, the objective function is a cost or an energy function that has to be minimized. Nevertheless, an objective function can also be a fitness or utility function that has to be maximized.

In the discrete setting, the segmentation task usually begins with an undirected graph, $\mathcal{G}(\mathcal{P}, \mathcal{E})$, that is composed of vertices $\mathcal{P}$ and undirected edges $\mathcal{E}$. Each node of the graph ($p \in \mathcal{P}$) represents a random variable ($f_i^p$) taking on different labels ($i \in \mathcal{L} = \{l_1, \cdots, l_k\}$) and each edge encodes the dependency between neighbouring variables. The corresponding optimization problem of (3) in the discrete domain is:

$$
\min_f \left\{ \sum_{pq \in \mathcal{N}_i} V(f_i^p, f_q^p) + \sum_{p \in \mathcal{P}} D_p(f_p) \right\}
$$

$$
\text{s.t. } \sum_{i \in \mathcal{L}} f_i^p = 1, \; \forall p \in \mathcal{P},
$$

where $V$ is the regularization term (pairwise term) that encourages spatial coherence by penalizing discontinuities between neighbouring pixels, $D$ is the data penalty term (unary term), $f \in \mathcal{B}^{\mathcal{L} \times \mathcal{P}}$ are the binary variables ($f_i^p = 1$ if pixel $p \in \mathcal{P}$ belongs to region $i \in \mathcal{L}$ and $f_i^p = 0$ otherwise) and $\mathcal{N}_i$ is the neighbourhood which is typically defined as nearest neighbour grid connectivity.

There are several advantages and drawbacks associated with discrete and continuous methods:

- **Parameter tuning:** in the continuous domain, PDE-based approaches typically require setting a step size during the optimization procedure. More formally, in the PDE community, it is stated that the Euler-Lagrange equation pro-
vides a sufficient condition for the existence of a stationary point of the energy functional. Let \( u \) be a differentiable labeling function in a continuous domain and \( E(u) \) be an energy functional. Then, the Euler-Lagrange equation applied to \( E \) is:

\[
\frac{\partial E}{\partial u} - \frac{d}{dx} \left( \frac{\partial E}{\partial u_x} \right) - \frac{d}{dy} \left( \frac{\partial E}{\partial u_y} \right) = 0 ,
\]

(8)

where \( u_x \) and \( u_y \) are the derivatives of \( u \) in \( x \) and \( y \) directions, respectively. The minimizer of \( E \) may be computed via the steady state solution of the following update equation:

\[
\frac{\partial u}{\partial t} = \frac{\partial E}{\partial u} ,
\]

(9)

where \( \partial t \) is an artificial time step size. A step size too large leads to a non-optimal solution and numerical instability, while a step size too small increases the convergence time. One way to ensure numerical stability during the optimization is to place an upper bound on the time step using the Courant-Friedrichs-Lewy (CFL) condition (Courant et al., 1967). Under some conditions, the optimal step sizes may be computed automatically as proposed by Pock and Chambolle (2011). On the other hand, in discrete domain, graph cuts-based methods do not require such parameter tuning and have proven to be numerically stable.

Note that other parameters in the segmentation energy function, including weighting parameters to balance the energy terms (e.g. \( \lambda \) in (2)) and hyper parameters within each energy term or objective (e.g. number of histogram bins in calculating the regional/data term) are common between continuous and discrete approaches. Setting parameters can be done based on training data (learning-based) (Gennert and Yuille, 1988; McIntosh and Hamarneh, 2007) or based on the image content Rao et al. (2010).

- **Termination criterion**: While graph-based methods have an exact termination criterion, finding a general-purpose termination criteria for PDE-based methods is difficult. Strategies for stopping the optimization procedure include performing a fixed number of iterations and/or iterating until the change in the solution or energy is smaller than a predefined threshold.

- **Metrication error**: Metrication error, also known as grid bias, is defined as the artifacts which appear in graph-based segmentation methods due to penalizing region boundaries only across axis aligned edges. Figure 3 compares the discrete and continuous version of a max-flow algorithm. As seen in Figure 3, the contours obtained by graph cuts are noticeably blocky in the areas with weak regional cues (weak data term), while the contours obtained by the continuous method are smooth. The discrete nature of graph-based methods makes it difficult to efficiently implement a convex regularizer like total variation in the discrete domain. Metrication error can be reduced in graph-based methods by increasing the graph connectivity, e.g. (Boykov and Kolmogorov, 2003), but that also increases memory usage and computation time. In contrast, within the continuous domain, there is no such limitation and regularizers can be implemented efficiently that makes the PDE approaches free from metrication error. Note that although approaches with continuous energy formulations do not induce metrication errors, due to the discrete nature of digital images, all continuous operations are estimated by their discrete versions in the implementation stage.

- **Parallelization**: Unlike PDE approaches that are easily parallelizable on GPUs, graph-based techniques are not straightforward to parallelize. As an example, the max-flow/min-cut, a core algorithm of many state-of-the-art graph-based segmentation methods, is a P-complete problem, which is probably not efficiently parallelizable (Goldschlager et al., 1982; Nieuwenhuis et al., 2013) due to two reasons: (1) augmenting path operations in min-cut/max-flow algorithms are interdependent as different augmentation paths can share edges; (2) the updates of the edge residuals have to be performed simultaneously in each augmentation operation as they all depend on the minimum capacity within the augmentation path (Nieuwenhuis et al., 2013). Several attempts have focused on parallelizing the max-flow/min-cut computation. Push-relabel algorithms (Boykov et al., 1998; Delong and Boykov, 2008) relaxed the first issue mentioned above but the update operations are still interdependent. Other techniques split the graph into multiple parts and obtained the global optimum by iteratively solving sub-problems in parallel (Strandmark and Kahl, 2010; Liu and Sun, 2010) while Shekhovtsov and Hlaváč (2013) combined the path augmentation and push-relabel techniques.

![Figure 3: Metrication artifacts. Brain segmentation using (a) classical max-flow algorithm or graph cuts (GC) and (b) combinatorial continuous max-flow (CCMF) (Couprie et al., 2011). (c,e) Zoomed regions of (a). (d,f) Zoomed regions of (b). (Images adopted from (Couprie et al., 2011))](image-url)
• Memory usage: With respect to memory consumption, the continuous optimization methods are often the winner. While continuous methods require few floating point values for each pixel in the image, the graphical models require an explicit storage of edges as well as one floating value for each edge. This difference becomes important when we deal with very large images and when the large number of graph edges required to be implemented, e.g. hundreds of millions pixels of microscopy images, and 3D volumes (Appleton and Talbot, 2006).

• Runtime: The runtime variance in graph-based methods is higher than PDE-based methods. For example, considering the α-expansion (Boykov et al., 2001) as a popular multi-label optimization technique, the number of max-flow problems that need to be solved highly depends on the input image and the chosen label order. In addition, the number of augmentation steps needed to solve a max-flow problem depends on the graph structure and edge residuals (Nieuwenhuis et al., 2013). On the other hand, PDE-based methods have less runtime variance as they perform the same computation steps on each pixel.

For more qualitative and quantitative comparisons between continuous and discrete domain, refer to (Nieuwenhuis et al., 2013; Couprie et al., 2011; Nosrati and Hamarneh, 2014).

3.4. Optimization: convex (submodular) vs. non-convex (non-submodular)

In the continuous domain of energy, a function may be classified as non-convex, convex, pseudoconvex or quasiconvex (Figure 4). Below, we define each of these terms mathematically.

An energy function $E : S \rightarrow \mathbb{R}$ is convex if

\begin{equation}
\forall S_1, S_2 \subseteq S \text{ and } 0 \leq \lambda \leq 1
E(\lambda S_1 + (1 - \lambda)S_2) \leq \lambda E(S_1) + (1 - \lambda)E(S_2).
\end{equation}

A set $S$ is a convex set if $S_1, S_2 \subseteq S$ and $0 \leq \lambda \leq 1 \Rightarrow \lambda S_1 + (1 - \lambda)S_2 \subseteq S$. If $E$ is differentiable in $S_1 \in S$, $E$ is said to be pseudoconvex at $S_1$ if

\begin{equation}
\nabla E(S_1) \cdot (S_2 - S_1) \geq 0, S_2 \in \Omega \Rightarrow E(S_2) \geq E(S_1).
\end{equation}

We call $E$ a quasiconvex function if

\begin{itemize}
  \item the energy domain $S$ is a convex set and
  \item the sub-level sets $S_\alpha = \{ s \in S | E(s) \leq \alpha \}$ are convex for all $\alpha$.
\end{itemize}

Pseudoconvex functions share the property of convex functions in that, if $\nabla E(S) = 0$, then $S$ is a global minimum of $E$. The pseudoconvexity is strictly weaker than convexity. In fact, every convex function is pseudoconvex. For example, $E(S) = S + S^3$ is pseudoconvex and non-convex. Also, every pseudoconvex function is quasiconvex, but the relationship is not commutative, e.g. $E(S) = S^3$ is quasiconvex and not pseudoconvex.

In this paper we focus on convex and non-convex optimization problems; more details on quasiconvex problems can be found in (dos Santos Gromicho, 1998). In the continuous domain, an optimization problem must meet two conditions to be a convex optimization problem: 1) the objective function must be convex, and 2) the feasible set must also be convex. The drawbacks associated with non-convex problems are that, in general, there is no guarantee in finding the global solution and results strongly depend on the initial guess-initialization. In contrast, for a convex problem, a local minimizer is actually a global minimizer and results are independent of the initialization. However, non-convex energy functional often give more accurate models (see Section 3.5).

The corresponding terminologies for convex and non-convex problems in the discrete domain are submodular and non-submodular (supermodular) problems, respectively. Let $E$ be a function of $n$ binary variables and $E(f_1, ..., f_n) = \sum_i E_i(f_i) + \sum_{i<j} E_{ij}(f_i, f_j)$. Then the discrete energy functional $E$ is submodular if the following condition holds:

$$E_{ij}(0, 0) + E_{ij}(1, 1) < E_{ij}(0, 1) + E_{ij}(1, 0).$$

For higher order energy terms, e.g. $E_{ijk}(f_i, f_j, f_k)$, $E$ is submodular if all projections $^1$ of $E$ of two variables are submodular (Kolmogorov and Zabin, 2004).

Submodular energies can be optimized efficiently via graph cuts. Greig et al. (1989) were the first to utilize min-cut/max-flow algorithms to find the globally optimal solution for binary segmentation in 1989. Later in 2003, Ishikawa (2003) generalized the graph cut technique to find the exact solution for a special class of multi-label problems (more detail on Ishikawa’s approach in Section 4.5).

In recent years, many efforts have been made to bridge the gap between convex and non-convex optimization problems in the continuous domain through convex approximations of non-convex models. Historically, the two-region segmentation problem (foreground and background) was convexified in 2006 by Chan et al. (2006) and the multi-region segmentation problem was convexified in 2008 by Chambolle et al. (2008) and

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\[^1\text{Suppose } E \text{ has } n \text{ binary variables. If } m < n \text{ of these variables are fixed, then we get a new function } E' \text{ of } n - m \text{ binary variables; } E' \text{ is called a projection of } E.\]
Pock et al. (2008) for the first time (additional details on continuous multi-region segmentation problem in Section 4.5).

3.5. Fidelity vs. Optimizability

In energy-based segmentation problems there is a trade-off between fidelity and optimizability (Hamarneh, 2011; McIntosh and Hamarneh, 2012; Ullén et al., 2013; Nosrati and Hamarneh, 2014). Fidelity describes how faithful the energy function is to the data and how accurate it can model and capture intricate problem details. Optimizability refers to how easily we can optimize the objective function and attain the global optimum.

Generally, the better the objective function models the problem, the more complicated it becomes and the harder it is to optimize. If we instead sacrifice fidelity to obtain a globally optimizable objective function, the solution might not be accurate enough for our segmentation purpose.

In the image segmentation literature, many works have focused on increasing the fidelity and improving the modeling capability of objective functions by (i) adding new energy terms, e.g. edge, region, shape, statistical overlap and area prior terms (Gloger et al., 2012; Shen et al., 2011; Andrews et al., 2011b; Bresson et al., 2006; Pluempiitwiryawej et al., 2005; Ayed et al., 2009, 2008); (ii) extending binary segmentation methods to multi-label segmentation (Vese and Chan, 2002; Mansouri et al., 2006; Rak et al., 2013); (iii) modeling spatial relationships between labels, objects, or object regions (Felzenszwalb and Veksler, 2010; Liu et al., 2008; Rother et al., 2009; Colliot et al., 2006; Gould et al., 2008); and (iv) learning objective function parameters (Alahari et al., 2010; Nowozin et al., 2010; Szummer et al., 2008; McIntosh and Hamarneh, 2007; Kolmogorov et al., 2007).

Other works chose to improve optimizability by approximating non-convex energies with convex ones (Lehmann et al., 2009; Bae et al., 2011a; Boykov et al., 2001; Chambolle et al., 2008).

An ideal method improves both optimizibility and fidelity without sacrificing either property (green contour in Figure 5).

3.6. Uncertainty and fuzzy/probabilistic vs. crisp labelling

In an MIS problem, ideally, we are interested in finding an optimal ground truth labeling for an image, where each label represents a single structure of interest. However, as medical images are approximate representations of physical tissues and due to noise coming from the internal body structures and/or imaging devices, it is often difficult to precisely define a ground truth labeling. Even the manual segmentation of an image by several experts have some degree of inter-expert (different experts) and intra-expert (same expert at different times) variability due to ambiguities in the image. Therefore, it is beneficial to encode uncertainty into segmentation frameworks (Koerkamp et al., 2010). This information can be used to highlight the ambiguous image regions so to prompt users’ attention to confirm or manually edit the segmentation of these regions.

Uncertainty in object boundaries may arise from numerous sources, including graded composition (Udupa and Grevera, 2005), image acquisition artifacts, partial volume effects. Therefore, various image segmentation methods have been intentionally designed to output probabilistic or fuzzy results to better capture uncertainty in segmentation solutions (Grady, 2006; Zhang et al., 2001). Figure 6 demonstrates an example of how uncertainty information can be observed in an energy function. $E_1$ and $E_2$ in Figure 6 are two 1-D energy functions with the same optimal solution. However, segmentations near the minimal solution in $E_1$ have very similar energy values (high uncertainty) as opposed to solutions near the same optimal point in $E_2$ (less uncertainty/more certain). In fact, under the energy $E_1$, a small perturbation in the image (e.g. additional noise) may change the segmentation result significantly. Given a probability distribution function over the label space, i.e. $P(x)$ in (4), one way to calculate the uncertainty at pixel $x$ is to use Shannon’s entropy as: $h(x) = -\sum P(x) \log_2(P(x))$. The entropy can be used as an energy term in a segmentation energy function. In this case, lower entropy corresponds to larger certainty and vice versa.

As stated in Section 3.2, in addition to crisp labelling where each pixel is mapped to exactly one object label, two common ways to encode uncertainty into a segmentation framework are the adoption of probabilistic and fuzzy labelling. In probabilistic labelling, the probability of each label at each pixel is reported (Wells III et al., 1996; Grady, 2006; Saad et al., 2008, 2010b; Changizi and Hamarneh, 2010; Andrews et al., 2011a,b). In contrast, a partial membership of each pixel belonging to each class of labels by a membership function is reported in fuzzy labelling (Bueno et al., 2004; Howing et al., 1997).
of membership to a label is proportional to the area covered by that label (Figure 7(c)).

We should emphasize that although in the continuous domain, image representation and energy formulations are continuous (Figure 2(a) and Figure 1(a)), implementation of these methods for image processing involves a discretization step (e.g., estimating a derivative by discrete forward difference). However, while the values of labels are discrete (e.g., integer values) in the discrete settings, label values in the continuous setting can be real-valued. Nevertheless, from the theoretical point of view, continuous models correspond to the limit of infinitely fine discretization.

4. Prior knowledge for targeted image segmentation

In this section, we review the prior knowledge information devised to improve image segmentation. Table 1 presents some of these important priors and compares them in terms of the nature of achievable solution due to a given formulation (i.e., globally vs. locally optimal), metrication error, domain of action (continuous vs. discrete), and other properties. We also created an interactive online database to categorize existing works based on the type of prior knowledge they use. We made our website interactive so that researchers can contribute to keep the database up to date. Figure 8 illustrates a snapshot of our online database showing different prior information that have been used in the literature for targeted image segmentation.

4.1. User interaction

Incorporating user input into a segmentation framework may be an intuitive and easy way for the users to assist with characterizing the desired object and obtain usable results. In an interactive segmentation system, the user input is used to encode prior knowledge about the targeted object. The specific prior knowledge that the user is considering is unknown to the method, but only the implication of such prior knowledge (e.g., pixel x must be part of the object) is passed on to the interactive algorithm. Given a high-level intuitive user interactive system, the end-user does not need to know about the low-level underlying optimization and energy function details.

User input can be incorporated in several ways, such as through: mouse clicking (or even via eye gaze (Sadeghi et al., 2009)) and to provide seed points, specifying the subsets of object boundary or specifying sub-regions (bounding boxes) that contain the object of interest. The work proposed by (Kass et al., 1988) is perhaps one of the early works to incorporate user interaction into the segmentation framework, where they enable users to enforce spring-like forces between snake’s control points to affect the energy functional and to push the snake out of a local minima into another more desirable location.

The first form of user input (providing seeds) involves user specifying labels of some pixels inside and outside the targeted object by mouse-clicking or brushing. This allows a user to enforce hard constraints on labeled pixels. For example, in a binary segmentation scenario in the discrete setting, one can
Table 1: Some important prior information for targeted image segmentation

| Method | Multi-object | Shape | Topology | Moments | Geometrical/region interaction | Spatial distance | Adjacency | No. of edge/labels | Model/Atlas | No grid artifact | Guarantees on global solution |
|--------|--------------|-------|----------|---------|-------------------------------|-----------------|-----------|-------------------|-------------|-----------------|-----------------------------|
| (Cootes et al., 1995) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Cootes and Taylor, 1995) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Rosen and Paragios, 2002) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Chen et al., 2002) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Tsai et al., 2003) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Slabaugh and Unal, 2005) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Zhu-Jacquot and Zabih, 2007) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Veksler, 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Song et al., 2010) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Andrews et al., 2010b) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Han et al., 2003) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Zeng et al., 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Vicente et al., 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Foulonneau et al., 2006) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Ayed et al., 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Kloot and Cremers, 2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Liu et al., 2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Wu et al., 2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Zhao et al., 1996) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Samson et al., 2000) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Li et al., 2006) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Zeng et al., 1998) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Goldenberg et al., 2002) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Paragiov, 2002) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Vazquez-Kema et al., 2009) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Ukewati et al., 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Rajchel et al., 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Delong and Boykov, 2009) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Ullén et al., 2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Schmidt and Boykov, 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Nosrati and Hamarnish, 2014) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Nosrati et al., 2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Nosrati and Hamarnish, 2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Liu et al., 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Felzenszwalb and Veksler, 2010) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Strekalovskiy and Creamers, 2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Strekalovskiy et al., 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Bergbauer et al., 2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Zhu and Yuille, 1996) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Brox and Weickert, 2006) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Ben Ayed and Mitiche, 2008) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Delong et al., 2012a) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Yuan et al., 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Iosifescu et al., 1997) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Collins and Evans, 1997) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Prisacariu and Reid, 2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Sandhu et al., 2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (Prisacariu et al., 2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
defined as: \( \delta \)

respectively. \( L \) represents inside and outside regions of the object of interest, where \( \delta \) is the Dirac delta function. The function \( \phi(x) \) is not marked. The user interaction term proposed by Ben-Zadok et al. (2009) is then defined as:

\[
E_{\text{user}}(x) = \int_{\Omega} \int_{\Omega'} (L(x') - H(\phi(x)))^2 K(x, x')dx'dx , \tag{18}
\]

where \( H \) is the Heaviside step function and \( N \) is the neighborhood of the coordinate \( x \). \( L(x) = 0 \) if the user’s click is within the segmented region and \( L(x) = 1 \) if the click is on the background. \( L(x) = H(\phi(x)) \) if \( x \) is not marked. The user interaction term proposed by Ben-Zadok et al. (2009) is defined as:

\[
E_{\text{user}}(\phi) = -\int_{\Omega} L(x) \text{sign} (\phi(x)) dx , \tag{14}
\]

Figures 8: Snapshot of our interactive online database of segmentation articles categorized by type of prior information devised in their framework (http://goo.gl/gy9pyn). Our online system allows users to update the records to ensure an up-to-date database.

enforce \( f^p_{\text{foreground}} = 1 \) if \( p \in \text{foreground} \) and \( f^p_{\text{background}} = 0 \) if \( p \in \text{background} \) in (7).

In the continuous domain, (Paragios, 2003), (Cremers et al., 2007) and (Ben-Zadok et al., 2009) have proposed level set-based methods in which a user can correct the solution interactively by clicking on incorrectly labelled pixels. Mathematically, let \( \phi \) be the level set function (often is represented by the signed distance map of the foreground) where \( \phi > 0 \) and \( \phi < 0 \) represent inside and outside regions of the object of interest, respectively. Cremers et al. (2007) proposed to add the following user interaction term to their energy functional consisting of other data and regularization terms:

\[
E_{\text{user}}(\phi) = -\int_{\Omega} L(x) \text{sign} (\phi(x)) dx , \tag{14}
\]

where \( L : \Omega \rightarrow \{-1, 0, +1\} \) reflects the user input and is defined as:

\[
L(x) = \begin{cases} +1 & \text{if } x \text{ is marked as 'object'} \\ -1 & \text{if } x \text{ is marked as 'background'} \\ 0 & \text{if } x \text{ is not marked} \end{cases} \tag{15}
\]

Ben-Zadok et al. (2009) also used a similar energy functional similar to (Cremers et al., 2007). Assuming that \( \{x_i\}_{i=1}^{n} \) denotes the set of user input, which indicates the incorrectly labelled regions, they defined \( M : \Omega \rightarrow [0, 1] \) as:

\[
M(z) = \sum_{i=1}^{n} \delta(z - x_i) , \tag{16}
\]

where \( \delta \) is the Dirac delta function. The function \( L : \Omega \rightarrow \mathbb{R} \) is defined as:

\[
L(x) = H(\phi(x)) + (1 - 2H(\phi(x))) \int_{\in\Omega} M(z)dz , \tag{17}
\]
is asked to draw a box around the targeted object. This bounding box can be provided automatically using machine learning techniques in object detection. In the discrete setting, GrabCut proposed by Rother et al. (2004) is one of the most well-known methods with this kind of initialization. Lempitsky et al. (2009) proposed a method which shows how a bounding box is used to impose a powerful topological prior that prevents the solution from excessively shrinking and splitting, and ensures that the solution is sufficiently close to each of the sides of the bounding box. Grady et al. (2011) performed a user study and showed that a single box input is in fact enough for segmenting the targeted object. In the continuous setting, this kind of user input (sub-region specification) is taken into account by methods like geodesic active contours (Caselles et al., 1997) in which the user initializes the active contour around the object of interest.

Similar interaction is utilized in 3D live-wire (Hamarneh et al., 2005) as implemented in the TurtleSeg software\footnote{www.turtleseg.org} (Top and et al., 2011; Top et al., 2011). In 3D live-wire, few slices in different orientations of a 3D volume are segmented using 2D live-wire. Then, the segmented 2D slices are used to segment the whole 3D volume by generating additional contours on new slices automatically. The new contours are obtained by calculating optimal paths connecting the points of intersection between the new slice planes and the original contours provided semi-automatically by the user.

Saad et al. (2010a) proposed another type of interactive image analysis in which a user is able to examine the uncertainty in the segmentation results and improve the results, e.g. by changing the parameters of their segmentation algorithm. For an expanded study on interaction in MIS, interested readers may refer to (Saad et al., 2010b,a).

4.2. Appearance prior

Appearance is one of the most important visual cues to distinguish between different structures in an image. Appearance is described by studying the distribution of different features such as intensity values in gray-scale images, color, and texture inside each object. In most cases, appearance models are incorporated into the data term in (2) and (7). The purpose of incorporating appearance prior is to fit the appearance distribution of the segmented objects to the distribution of objects of interest, e.g. using Gaussian mixture model (GMM) (Rother et al., 2004). In the literature, there are two ways to model the appearance: 1) adaptively learning the appearance during the segmentation procedure, and 2) knowing the appearance model prior to performing segmentation (e.g. by observing the appearance distribution of the training data). In the former case, the appearance model is learned and estimated from the distribution of features inside small samples of each object. Figure 9 illustrates the probability of different structures (the kidney, the tumour, and the background) in an endoscopic scene. A lower intensity in (b-d) corresponds to higher probability.

To fit the segmentation appearance distribution to the prior distribution, a dissimilarity measure \( d \) is usually needed where \( d(g_i, \hat{g}_i) \) measures the difference between the appearance distribution of \( i^{th} \) object \( g_i \) and its corresponding prior distribution \( \hat{g}_i \). This dissimilarity measure can be encoded into the energy functional (2) directly as the data term or via a probabilistic formulation. For example, consider the appearance prior of an object in a scalar-valued image \( I \), then \( g_i \) would be the mean \( (\mu_i) \) and variance \( (\sigma_i^2) \) of the intensities of the targeted object. Then, assuming a Gaussian approximation of the object’s intensity \( I \), the corresponding probability distribution will be:

\[
P(x|\hat{g}_i) = \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-\frac{(x-\mu_i)^2}{2\sigma_i^2}}. \tag{19}
\]

Other than scalar-valued medical images such as MR (Pluemppitwiriyawej et al., 2005) and US (Noble and Boukerroui, 2006), appearance models can be extracted from other types of images like color image (e.g. skin (Celebi et al., 2009), endoscopy (Figueiredo et al., 2010), microscopy (Nosrati and Hamarneh, 2013)), other vector-valued images (dynamic positron emission tomography, dPET, (Saad et al., 2008)), and tensor-valued or manifold-valued images (Federn et al., 2003; Wang and Vemuri, 2004; Weldeselassie and Hamarneh, 2007). For the vector-valued images, one can use multivariate Gaussian density as an appearance model. The formulation is similar to (19) with the use of the covariance matrix \( \Sigma \) instead of \( \sigma_i^2 \). Regarding the tensor-valued images, several distance measures in the space of tensors have been proposed such as:
• Log-Euclidean tensor distance is defined as:

\[ d_{LE}(T_i, \hat{T}_i) = \sqrt{\text{trace}((\log(T_i) - \log(\hat{T}_i))^2)}. \]

where \(T_i\) and \(\hat{T}_i\) are a tensor from \(i^{th}\) region and its corresponding prior tensor model, respectively.

• The symmetrized Kulback-Leibler (SKL) divergence (also known as J-convergence) (Wang and Vemuri, 2004) is defined as:

\[ d_{SKL}(T_i, \hat{T}_i) = \frac{1}{2} \sqrt{\text{trace}(T_i^{-1}\hat{T}_i + \hat{T}_i^{-1}T_i) - 2n}, \]

where \(n\) is the size of the tensor \(T_i\) and \(\hat{T}_i\) (\(n = 3\) in DT-MRI). This measure is affine invariant.

• The Rao distance (Lenglet et al., 2004) is defined as:

\[ d_R(T_i, \hat{T}_i) = \frac{1}{2} \text{log}^2(\lambda_i), \]

where \(\lambda_i\) denotes the eigenvalues of \(T_i^{-1/2}\hat{T}_iT_i^{-1/2}\).

Intensity and color information are not always sufficient to distinguish different objects. Hence, several methods proposed to model objects with more complex appearance using texture information as a complementary feature (Huang et al., 2005; Malcolm et al., 2007; Santner et al., 2009).

Bigun et al. (1991) introduced a simple texture feature model consists of the Jacobian matrix convolved by a Gaussian kernel \((K_\sigma)\) that results in three different feature channels, i.e. in case of a 2D image the features are \(K_\sigma \ast (I_i^2, I_i, I_i^0)\). However, these features ignore the non-textured object that might be of interest. Therefore, Rousson et al. (2003) proposed to use the following texture features in order to segment objects with and without texture: \((I, I^2, I^0, I^2, I^0, I^0)\).

More advanced texture features such as those based on Haar and Gabor filter banks have shown many successes in medical image segmentation (Huang et al., 2005; Malcolm et al., 2007; Santner et al., 2009). Koss et al. (1999) and Frangi et al. (1998) are two works that utilized advanced features to segment abdominal organs and to measure vesselness, respectively. In (Frangi et al., 1998), the eigenvalues of the image Hessian matrix are used for measuring the vesselness of pixels in images. This measure is used for liver vessel segmentation both in a variational framework (Freieman et al., 2009) and in a graph-based framework (Esmaeili et al., 2010). Statistical overlap prior is another strong appearance prior that has been proposed by Ayed et al. (2009). Their method embeds statistical information (e.g. histogram of intensities) about the overlap between the distributions within the object and the background in a variational image segmentation framework. They used the Bhattacharyya coefficient measuring the amount of overlap between two distributions, i.e. \(d_B(g(z), \hat{g}(z)) = \sum_z \sqrt{g(z)\hat{g}(z)} \forall z \in Z\) if \(I : \Omega \rightarrow \mathbb{Z}\). Ben Ayed et al. (2009) used this strong prior to segment left ventricle in MR images.

Other features such as frequency, bag of visual words, gradient location and orientation histogram (GLOH) (Mikolajczyk and Schmid, 2005), DAISY (Tola et al., 2008), GIST (spatial envelop) (Oliva and Torralba, 2001), local binary pattern (LBP) (Heikkilä et al., 2009), SURF (Bay et al., 2006), histogram of oriented gradient (HOG) (Dalal and Triggs, 2005), and scale invariant feature transform (SIFT) (Lowe, 2004) are sometimes helpful as appearance features (Bosch et al., 2007).

Sometimes the appearance of structures is too complicated that regular features cannot describe them accurately. To extract the appearance characteristics of such structures different machine learning techniques have been proposed. These machine learning techniques learn the appearance either by combining several features like texture, color, intensity, HOG, etc., and feed the combined feature vectors to a classifier like random forest decision forest (RF) or support vector machine (SVM) (Tu et al., 2006; Nosrati et al., 2014), or by learning a dictionary which describes the object of interest (Mairal et al., 2008; Nieuwenhuis et al., 2014; Nayak et al., 2013).

In general, appearance features can be extracted in the following domains based on the type of the medical data:

• **spatial domain**: several methods have been developed to segment 2D or 3D static images (Chan et al., 2000; Cootes et al., 2001; Vese and Chan, 2002; Feddern et al., 2003; Wang and Vemuri, 2004; Huang et al., 2005; Malcolm et al., 2007; Santner et al., 2009);

• **time domain**: in dynamic medical images, it is beneficial to consider the temporal dimension along with the spatial dimensions. For example, extracting appearance features in temporal direction would be very informative in dynamic positron emission tomography (dPET) images, where each pixel in the image represents a time activity curve (TAC) that describes the metabolic activity of a tissue as a result of tracer uptake (Saad et al., 2008). Other examples include (Mirzaei et al., 2013) where spatiotemporal features are used to distinguish tumour regions in 4D lung CT (3D+time) and (Amir-Khalili et al., 2014) where the likelihood of vessel regions are calculated based on temporal and frequency analysis.

• **scale domain**: for some objects with more complex texture, it is useful to estimate the appearance model in different scales for more accurate results and ensure that the model is scale invariant (Han et al., 2009; Mirzaalain and Hamarneh, 2010).

Regardless of where the appearance information comes from, it is encoded through a data energy term \((D)\) that assigns each pixel a probability of belonging to each class of objects (5).

4.3. Regularization

The regularization term corresponds to priors on the space of feasible solutions. Several regularization terms have been proposed in the literature. The most famous one is the Mumford-Shah model (Mumford and Shah, 1989) that penalizes the boundary length of different regions in a spatially continuous domain, i.e. \(\sum_{x \in \Omega} |\partial I(x)|\). The corresponding regularization model in the discrete domain is Pott’s model that penalizes
any appearance discontinuity between neighbouring pixels and is defined as \( \sum_{j \in S} w_{ij} \delta(I_j \neq I_i) \).

The regularization term formulated in the discrete setting is biased by the discrete grid and favours curves to orient along with the grid, e.g. in horizontal and vertical or diagonal directions in a 4-connected lattice of pixels. As mentioned in Section 3.3, this produces grid artifacts, also known as metrication error (Figure 3). On the other hand, the regularization term in the continuous settings allows one to accurately represent geometrical entities such as curve length (or surface area) without any grid bias.

Some other regularization terms in continuous domain, written in the level set notation (\( \phi \)), are listed as follows:

- **Length regularization:** \( \int_{\Omega} |\nabla H(\phi(x))| dx \), where \( H(.) \) is the Heaviside step function.

- **Total variation (TV):** \( \int_{\Omega} |\nabla \phi(x)| dx \), which only smooths the tangent direction of the level set curve. This term is used especially when a single function \( \phi \) is used to segment multiple regions, i.e. \( \phi \) is not necessarily a signed distance function. It is worth mentioning that there are two variants of the total variation term: the isotropic variant using \( \ell_2 \) norm,

\[
\int_{\Omega} |\nabla \phi(x)|_2 dx = \int_{\Omega} \sqrt{\phi_{xx}^2 + \cdots + \phi_{xy}^2} dx ,
\]

and the anisotropic variant using \( \ell_1 \) norm,

\[
\int_{\Omega} |\nabla \phi(x)|_1 dx = \int_{\Omega} |\phi_{xx}| + \cdots + |\phi_{xy}| dx .
\]

The anisotropic version is not rotationally invariant and therefore favours results that are aligned along the grid system. The isotropic version is typically preferred but cannot be properly handled by discrete optimization algorithms as the derivatives are not available in all directions in the discrete settings.

- **\( H^1 \) norm:** \( \int_{\Omega} |\nabla \phi(x)|_1^2 dx \), which applies a purely isotropic smoothing at every pixel \( x \).

A comparison of the above mentioned regularization terms can be found in (Chung and Vese, 2009).

Higher order regularization terms were also proposed to encode more constraints on the optimization problem. For example, Duchenne et al. (2011) introduced the ternary term (along with unary and pairwise terms in the standard MRF) for graph matching (and not image segmentation) application and Delong et al. (2012b) proposed an efficient optimization framework to optimize sparse higher order energies in the discrete domain.

Curvature regularization is another useful type of regularization that has been shown to be capable of capturing thin and elongated structures (Schoenemann et al., 2009; El-Zehiry and Grady, 2010). In addition, there is evidence that cells in the visual cortex are responsible for detecting curvature (Dobbins et al., 1987).

While curvature regularization term can be easily formulated in the local optimization frameworks, e.g. in a level set formulation (Leventon et al., 2000a) and Snakes’ model (Kass et al., 1988), it is much more difficult to incorporate such prior in a global optimization framework. Strandmark and Kahl (2011) proposed several improvements to approximate curvature regularization within a global optimization framework. They defined the curvature term as: \( \int_{\partial R} k(x)^2 dx \), where \( \partial R \) is the boundary of the foreground region and \( k \) is the curvature function. They approximated the above mentioned curvature term with discrete computation techniques by tessellating the image domain into a cell complex, e.g. hexagonal mesh, which is a collection of non-overlapping basic regions whose union gives the whole domain. They recast the problem as an integer linear program (along with a data term and length/area regularization terms) and optimized the total energy via linear programming (LP) relaxation. Figure 10(a) shows how Strandmark and Kahl (2011) discretized the image domain by cells. If \( f_i, i = 1, \cdots, m \) denotes binary variables associated to each cell region and \( e_i \) denotes the boundary variable, then the curvature regularization term is written as a linear function: \( \sum_{i,j} b_{ij} e_{ij} \), where \( e_{ij} \) denotes the boundary pairs and

\[
b_{ij} = \min(l_i, l_j) \left( \frac{\alpha}{\min(l_i, l_j)} \right)^2 ,
\]

where \( l_i \) is the length of edge \( i \) and \( \alpha \) is the angle difference between two lines. Later, Strandmark et al. (2013) extended their previous work (Strandmark and Kahl, 2011) and proposed a globally optimal shortest path method that minimizes general functionals of higher-order curve properties, e.g. curvature and torsion. Figure 10(b) illustrates the usefulness of curvature prior on vessel segmentation.

### 4.4. Boundary information

Boundary and edge information is a powerful feature for delineating the objects of interest in an image. To incorporate such information, it is often assumed that the object boundaries are more likely to pass between pixels with large intensity/color contrast or, more generally, regions with differ-
ent appearance (as captured by any of the measures in Section 4.2). As object boundaries are locations where we expect discontinuities in the labels, this information is usually linked to the regularization term in (2) such that the regularization penalty is decreased in high contrast regions (most likely objects’ boundaries) to allow for discontinuity in labels. The functions \( w_{ij} = \exp(-\beta ||I_i - I_j||^2) \) and \( w'_{ij} = 1/1 + \beta ||I_i - I_j||^2 \) are two examples of a boundary weighting function where \( I_i \) and \( I_j \) represent the intensity/color value associated with pixels \( i \) and \( j \) in image \( I \), respectively (Grady, 2012). These boundary weights are used as multiplication factors along with the regularization term mentioned in Section 4.3. Geodesic active contour (Caselles et al., 1997), normalized-cut (Shi and Malik, 2000), and random walker (Grady, 2006) are three examples that employed such boundary weighting technique.

Boundary and edge information can also be linked to the data term in (2) via the use of edge detectors, which typically involve first and second order spatial differential operators. Several methods have been proposed to calculate first and second order differences in scalar images (Canny, 1986; Frangi et al., 1998) and color images (Shi et al., 2008; Tsai et al., 2002). However, some medical images are manifold-valued (e.g. DT MRI). To address this, Nand et al. (2011) extended the first order differential as \( g(x) = \sqrt{I(x)} \) where \( \lambda \) and \( \hat{e} \) are respectively the largest eigenvalue and eigenvector of \( S(x) = J(x)^T J(x) \) and \( J(x) \) is the Jacobian matrix generalizing the gradient of a scalar field to the derivatives of the 3D DT image. Similarly, the authors extended the second order differential as \( G(x) = \frac{G(x)G(x)^T}{2} \) where \( G(x) \) is the Jacobian matrix of \( g(x) \), i.e. \( G_{ij} = \frac{
abla g_{ij}}{\sqrt{g}} \). Similar approach has been proposed for boundary detection in color images, e.g. in color snakes (Sapiro, 1997) and in detecting boundaries of oral lesions in color images (Chodorowski et al., 2005).

**Boundary polarity:** A problem with the aforementioned boundary models is that they describe a boundary point that passes between two pixels with high image contrast without accounting for the direction of the transition (Boykov and Funka-Lea, 2006; Grady, 2012). Singaraju et al. (2008) considered the transition direction in boundary detection. For example, it is possible to distinguish between boundaries from bright to dark and from dark to bright (boundary polarity). This boundary polarity is incorporated into a graph-based framework by replacing each undirected edge, \( e_{ij} \), by two directed edges, \( e_{ij}^+ \) and \( e_{ij}^- \), with edge weight calculated as:

\[
E = \sum_{p \in \mathcal{P}} D_p(f_p) + \sum_{(p,q) \in \mathcal{N}} V_{pq}(f_p, f_q) ,
\]

where \( \mathcal{P} \) is the set of all pixels, \( f = \{ f_p | p \in \mathcal{P} \} \) is a labeling of the image, \( D_p(f_p) \) measures how well label \( f_p \) fits pixel \( p \) and \( V_{pq} \) is a penalty term for every pair of neighbouring pixels \( p \) and \( q \) that encourages neighbouring pixels to have the same label. The second term ensures that the segmentation boundary is smooth. The methods proposed in (Boykov et al., 2001) require \( V_{pq} \) to be either a metric or semimetric. \( V \) is a metric appearance and not for textured objects. One possible way to address these aforementioned issues (low contrast image and textured objects) is to utilize the piecewise constant case of Mumford-Shah model (Mumford and Shah, 1989) and replace \( I \) with \( \tau(I) \), where \( \tau \) is a function that maps the pixel content to a transformed space where the object appearance is relatively constant (Grady, 2012). The Mumford-Shah model segments the image into a set of pairwise disjoint regions with minimal appearance variance and minimal boundary length. Among the most popular methods that adopted the Mumford-Shah model is the active contours without edges (ACWOE) method proposed by Chan and Vese (2001). As an example (Sandberg et al., 2002) proposed a level set-based active contour algorithm to segment textured objects. Another example is the work proposed by Paragios and Deriche (2002) where boundary and region-based segmentation modules were exploited and unified into a geodesic active contour model to segment textured objects.

4.5. Extending binary to multi-label segmentation

In many medical image analysis problems, we are often interested in segmenting multiple objects (e.g. segmenting retinal layers from optical coherence tomography (Yazdanpanah et al., 2011)). Unlike a large class of binary labeling problems that can be solved globally, multi-label problems, on the other hand, cannot be globally minimized in general. In 2001, Boykov et al. (2001) proposed two algorithms (\( \alpha \)-expansion and \( \alpha \)-\( \beta \) swap) based on graph cuts that efficiently find a local minimum of a multi-label problem. They consider the following energy functional:

Figure 11: Cardiac right ventricle segmentation (a) without encoding edge polarity and (b) with encoding edge polarity by specifying the bright to dark edges as the desired ones. Note how the incorrect boundary transition (the yellow arrow) in (a) has been corrected in (b) by specifying boundary polarity.
on the space of labels $\mathcal{L}$ if it satisfies the following three conditions:

$$V(\alpha, \beta) = 0 \iff \alpha = \beta$$  \hspace{1cm} (25)
$$V(\alpha, \beta) = V(\beta, \alpha) > 0$$  \hspace{1cm} (26)
$$V(\alpha, \gamma) \leq V(\alpha, \gamma) + V(\gamma, \beta),$$  \hspace{1cm} (27)

for any labels $\alpha, \beta, \gamma \in \mathcal{L}$. If $V$ only satisfies (25) and (26) then $V$ is a semimetric. Boykov et al. (2001) find the local minima by swapping a pair of labels ($\alpha$-$\beta$-swap) or expanding a label ($\alpha$-expansion) and evaluate the energy using graph cuts iteratively. Later in 2003, Ishikawa (Ishikawa, 2003) showed that, if $V_{pq}(f_p, f_q)$ is convex and symmetric in $f_p - f_q$, one can compute the exact solution of the multi-label problem. Ishikawa used the following formulation:

$$E(f) = \sum_{p \neq p'} D(f_p) + \sum_{(p,q) \in \mathcal{N}} g(\ell(f_p) - \ell(f_q)),$$  \hspace{1cm} (28)

where $D(.)$ in the first term (data term) is any bounded function that can be non-convex, $g(.)$ is a convex function, and $\ell$ is a function that gives the index of a label, i.e. $\ell(\text{label } i) = i$. The term $g(\ell(f_p) - \ell(f_q))$ expresses that there is a linear order among the labels and the regularization depends only on the difference of their ordinal number. Ishikawa showed that if $g(.)$ is convex in terms of a linearly ordered label set, the problem of (28) can be exactly optimized by finding the min-cut over a specially constructed multi-layered graph in which each layer corresponds to one label.

In the continuous domain, Vese and Chan (2002) extended their level set-based method to multiphase level sets. To segment $N$ objects, their method needs $\lceil \log_2 N \rceil$ level set functions. The number of regions is upper-bounded by a power of two (Figure 12(a)). Therefore, the actual number of regions the method yields is sometimes not clear as it depends on the image and the regularization weights. This issue happens specifically when the number of regions of interest is less than $2^{\lceil \log_2 N \rceil}$. Mansouri et al. (2006) proposed to assign an individual level set function to each object of interest (excluding the background), i.e. their method needs $N - 1$ non-overlapping level set functions to segment $N$ objects (Figure 12(b)). Chung and Vese (2009) proposed another method that uses a single level set function for multi-object segmentation. They proposed to use different layers (or levels) of a level set function to represent different regions as opposed to just using the zero level set (Figure 12(c)). None of the aforementioned continuous methods guarantee a globally optimal solution for multi-label problems. Pock et al. (2008) proposed a spatially continuous formulation of Ishikawa’s multi-label problem. In their method, the non-convex variational problem is reformulated as a convex variational problem via a technique they called functional lifting. They used the following energy functional

$$E(u) = \int_{\Omega} \rho(u(x), x)dx + \int_{\Omega} |\nabla u(x)|dx,$$  \hspace{1cm} (29)

which can be seen as the continuous version of Ishikawa’s formulation (24). $u : \Omega \rightarrow \Gamma$ in (29) is the unknown labeling function and $\Gamma = [\gamma_{min}, \gamma_{max}]$ is the range of $u$. The first term in (29) is the data term, which can be a non-convex function, and the second term is the total variation regularization term which is a convex term. In the functional lifting technique, the idea is to transfer the original problem formulation to a higher dimensional space by representing $u$ in terms of its super level sets $\phi$ defined as:

$$\phi(x, \gamma) = \begin{cases} 
1 & \text{if } u(x) > \gamma \\
0 & \text{otherwise} 
\end{cases}.$$  \hspace{1cm} (30)

Now, (29) can be re-written in terms of the super level set function as

$$E(\phi) = \int_{\Sigma} \rho(\phi(x, \gamma))|\partial_{\gamma}(\phi(x, \gamma))|d\Sigma + \int_{\Sigma} |\nabla \phi(x, \gamma)|d\Sigma,$$  \hspace{1cm} (31)

which is convex in $\phi$ and $\Sigma = [\Omega \times [0,1)]$. The minimization of $E(\phi)$ is not a convex optimization problem since $\phi : \Sigma \rightarrow [0,1]$. Hence, $\phi$ is relaxed to vary in $[0,1]$. We emphasize that the method of Pock et al. cannot always guarantee the globally optimal solution of the original problem (before $\phi$ is relaxed and when $\phi$ is binary). Brown et al. (2009) utilized functional lifting technique proposed by (Pock et al., 2008) and proposed a dual formulation for the multi-label problem. Their method guarantees a globally optimal solution. Recently, inspired by Ishikawa, Bae et al. (2011b) proposed a continuous max-flow model for multi-labeling problem via convex relaxed formulations. Not only can their continuous max-flow formulations obtain exact and global optimizers to the original problem, but they also showed that their method is significantly faster than the primal-dual algorithm of Pock et al. (2008).

### 4.6. Shape prior

Shape information is a powerful semantic descriptor for specifying targeted objects in an image. In our categorization, shape prior can be modelled in three ways: geometrical (template-based), statistical, and physical.

#### 4.6.1. Geometrical model (template)

Sometimes the shape of the targeted object is known a priori (e.g. ellipse or cup-like shape). In this case, the shape can be modelled either by parametrization (e.g. an ellipse can be parametrized by its center coordinate, major and minor radius and orientation) or by a non-parametric way (e.g. by its level...
set representation) and incorporated into a segmentation framework.

One way to incorporate a geometrical shape model into a segmentation framework is to penalize any deviation from the model. In the continuous domain, given two shapes represented by their signed distance functions $\phi_1$ and $\phi_2$, a simple way to calculate the dissimilarity between them is given by $\int_\Omega (\phi_1 - \phi_2)^2 dx$. The problem with this measure is that it depends on $\Omega$, i.e. as the size of $\Omega$ is increased, the difference becomes larger. An alternative is to constrain the integral to the domain of $\phi_1$, i.e. $\int_\Omega (\phi_1 - \phi_2)^2 H(\phi_1) dx$, as proposed in (Rousson and Paragios, 2002). The aforementioned formulas are usable if the pose of the object of interest (location, rotation and scale) is known. If the pose of an object is unknown, one can include the pose parameters into the shape energy term and optimize the energy functional with respect to both pose parameters and the level set. For example, the authors in (Chen et al., 2002) imposed the shape prior on the extracted contour after each iteration of their level set-based algorithm. Pluempitiwiriyawej et al. (2003) also described the shape of an ellipse with five parameters that include its pose parameters and optimized their energy functional by iterating between optimizing the shape energy term and the regional term.

In the discrete domain, the method of Slabaugh and Unal (2005) is one of the primary works to incorporate an explicit shape model into a graph-based segmentation framework. They proposed the following extra term (in addition to data and regularization terms) that constrained the segmentation to return an elliptical object:

$$E_{\text{ellipse}}(f, \theta) = \sum_{i \in P} |M_i^\theta - f_i|,$$  \hspace{1cm} (32)

where $M_i^\theta$ is the mask of an ellipse parametrized by $\theta$. As minimizing such a term is not straightforward, the authors optimize the energy functional iteratively, i.e. by finding the best $f$ for a fixed $\theta$ and then optimizing $\theta$ for a fixed $f$. For complex shapes that are hard to parametrize, an alternative approach is to fit a shape template to the current segmentation as proposed in (Freedman and Zhang, 2005). Veksler (2008) proposed to incorporate a more general class of shapes, known as star shapes, into graph-based segmentation. In Veksler’s work, it is assumed that the center point $(c)$ of the object is given. According to their definition, “an object has a star shape if for any point $p$ inside the object, all points on the straight line between the center $c$ and $p$ also lie inside the object” (Figure 13). The following pairwise term was introduced to impose the star shape prior:

$$E_{\text{star}}(f_p, f_q) = \begin{cases} 0 & \text{if } f_p = f_q \\ \infty & \text{if } f_p = 1 \text{ and } f_q = 0 \\ \beta & \text{if } f_p = 0 \text{ and } f_q = 1 \end{cases}.$$ \hspace{1cm} (33)

This prior is particularly useful for segmentation of convex objects, e.g. optic cup and disc segmentation (Bai et al., 2014).

4.6.2. Statistical model

In many practical applications, objects of the same class are not identical or rigid. For example, in medical images, the shape of organs vary from one subject to another or even over time and so, assuming a fixed shape template may be inappropriate. A typical way to capture the intra-class variation of shapes is to build a shape probability model, i.e. $P(\text{shape})$. Now, two questions have to be investigated: 1) how to represent a shape; explicitly (e.g. point cloud), implicitly (e.g. level set), boundary-based (e.g. surface mesh) or medial-based (e.g. m-reps (Pizer et al., 2003)), and 2) what probability distribution model to adopt, e.g. Gaussian distribution, Gaussian mixture model, or kernel density estimation (KDE).

Cootes et al. (1995) generated a compact shape representation and performed PCA (assuming Gaussian distribution) on a set of training shapes to obtain the main modes of variation. The idea is to model the plausible deformations of object’s shape ($S$) by its principal modes of variation:

$$S = \mathcal{S} + \sum_{i=1}^k w_i P_i,$$ \hspace{1cm} (34)

where $\mathcal{S}$ is the average shape, $P_i$ is the $i^{th}$ principal component and $w_i$ is its corresponding weight (or shape parameter). Cootes et al. (1995) used object’s coordinates to represent $S$. Given an initial estimation of the position of an object, the segmentation is performed by directly optimizing an energy functional over the weights $w_i$. This model is later improved by Tsai et al. (2001, 2003); Leventon et al. (2000b) and Van Ginneken et al. (2002). For example, Leventon et al. (2000b) represent $S$ by its level sets to automatically handle topological changes during the contour evolution. Tsai et al. (2003) used the same level set-based shape representation as Leventon et al. (2000b) and incorporated the shape prior in a region-based energy functional as opposed to an edge-based energy proposed in (Cootes et al., 1995). Van Ginneken et al. (2002) proposed to use a general set of local image structure descriptors including the moments of local histograms instead of the normalized first order derivative profiles used in Collins et al. (1995).

Similar to Tsai et al. (2003) in the continuous domain, Zhu-Jacquot and Zabih (2007) employed an iterative approach that accounts for shape variability in a graph-based setting. At each iteration, they optimize the weights of principal modes of
variations and the set of rigid transformation parameters given
to a tentative segmentation. Then, the segmentation is updated
given the fitted shape template by minimizing an energy func-
tional consisting of a regional term. The procedure is repeated
until convergence. Recently, Andrews et al. (2014) proposed
a probabilistic framework and incorporated shape prior to seg-
ment multiple anatomical structures. They utilized PCA in the
isometric log-ratio space as PCA assumes that the probabilistic
data lie in the unconstrained real Euclidean space. This is not
a valid assumption as the sample space for a probabilistic data
is the unit simplex and PCA may generate invalid probabilities,
and hence, invalid shapes.

In the above mentioned methods based on PCA, aligning the
shapes before computing the principal modes of variation is
necessary and to perform this alignment, it is often needed to
provide point-to-point correspondences between landmarks of
different subjects. This might be a tedious task. Hence, some
methods proposed to capture shape variations in the frequency
domain by representing shapes with the coefficients of its
discrete cosine transform (DCT) (Hamarneh and Gustavsson,
2000), Fourier transform (Staib and Duncan, 1992) or spheri-
cal wavelet transform (Nain et al., 2006).

While PCA is a popular linear dimensionality reduction tech-
nique, it has the restrictive assumption that the input data is
drawn from a Gaussian distribution. If the shape variation does
not follow a Gaussian distribution, we might end up with invalid
shapes or unable to represent valid shapes. In this case, a more
accurate estimation of shape parameters might be obtained by
Gaussian mixture models as proposed in (Cootes and Taylor,
1999). In addition, PCA is only capable of describing global
shape variations, i.e., changing a parameter corresponding to
one eigenvector deforms the entire shape, which makes it diffi-
cult to obtain a proper local segmentation. To control the sta-

tistical shape parameters locally, Davatzikos et al. (2003)

presented a hierarchical formulation of active shape models us-
ing the wavelet transform. Their wavelet-based encoding of
deformable contours is followed by PCA analysis. The statis-
tical properties extracted by PCA are then used as priors on
the contour’s deformation, some of which capture global shape
characteristics of the object boundaries while others capture lo-

cal and high-frequency shape characteristics. Hamarneh et al.
(2004) also proposed a method to locally control the statisti-

cal shape parameters. They used the medial-based profile for
shape representation and developed spatially-localized feasible
deformations using hierarchical (multi-scale) and regional
(multi-location) PCA and deform the medial profile at certain
locations and scales. Uzümcü et al. (2003) proposed to use in-
dependent component analysis (ICA) instead of PCA which
does not assume a Gaussian distribution of the input data and
can better capture localized shape variations. However, ICA
representation for shape variability is not as compact as PCA.

Ballester et al. (2005) proposed to use principal factor analysis
(PFA) as an alternative to PCA. PFA represents the observed D-
dimensional data $O$ as a linear function $\mathbf{F}$ of an L-dimen-
sional ($L < D$) latent variable $z$ and an independent Gaussian noise $\boldsymbol{e}$ as:

$$
\mathbf{F}(O) = \Lambda z + \mu + \text{err},
$$

where $\Lambda$ is the $D \times L$ factor loading ma-

trix defining the linear function $\mathbf{F}$, $\mu$ is a $D$-dimensional vector
representing the mean of the distribution of $O$, and $\text{err}$ is a $D$-
dimensional vector representing the noise variability associated
with each of the $D$ observed variables. As PFA models covari-
ance between variables and generates “interpretable” modes of
variation, while PCA determines the factors that account for
the total variance, (Ballester et al., 2005) argued that PFA is not
only adequate for the study of shape variability but also gives
better “interpretability” than PCA, and thus conclude that PFA
is better suited for medical image analysis.

Nevertheless, both PCA and ICA are linear factor anal-
ysis techniques, which make them difficult to model non-
linear shape variations. Techniques such as kernel PCA
(Schölkopf et al., 1998) and kernel density estimation (KDE)
are two alternatives to describe non-linear data. The works
proposed by (Cremers et al., 2006; Kim et al., 2007; Lu et al.,
2012) are examples that used non-linear dimensionality reduc-
tion techniques (e.g. kernel PCA and KDE) to incorporate
shape priors into image segmentation frameworks. For more
information about other linear and non-linear factor analysis
techniques, we refer to (Fodor, 2002; Bowden et al., 2000).

In addition to representing shapes as a set of points (as usu-
ally done in e.g. PCA cf. (34)), shapes can be described by
distance and angle information between different anatomical
landmarks (Wang et al., 2010; Namubkash et al., 2013).
For example, Wang et al. (2010) proposed a scale-invariant shape
description by measuring the relative distances between pair
of landmarks in a triplet, while Namubkash et al. (2013) model
the left ventricle (LV) shape in the cardium by calculating the
distance between each point on the surface of the LV and a re-
ference point in the middle of the LV provided by a user. More
reviews on statistical shape models for 3D medical image seg-
mentation can be found in (Heimann and Meinzer, 2009).

Beside the aforementioned statistical methods, some meth-
ods employed learning algorithms to impose a shape model into
segmentation (Zhang et al., 2012; Kawahara et al., 2013). In
(Zhang et al., 2012), authors proposed a deformable segmenta-
tion method based on sparse shape composition and dictionary
learning. In another work, Kawahara et al. (2013) augmented
the auto-context method (Tu and Bai, 2010) and trained se-
quential classifiers for segmentation. Auto-context (Tu and Bai,
2010) is an iterative learning framework that jointly learns the
appearance and regularization distributions where the predicted
labels from the previous iteration are used as input to the current
iteration. (Kawahara et al., 2013) used auto-context to learn
what shape-features (e.g. volume of a segmentation) a good
segmentation should have.

4.6.3. Physical model

In some medical applications, the biomechanical characteris-
tics of tissues can be estimated so that the physical characteris-
tics of tissues can be modeled in a segmentation framework as
additional prior information, thereby leading to more reliable
segmentations.

The incorporation of material elasticity property into image
segmentation was first introduced in 1988 by Kass et al. (1988)
in which spring-like forces between snake’s points is enforced.
Following Kass’ snakes model, several researchers also examined ways to extract vibrational (physical) modes of shapes based on finite element method (FEM); these include methods proposed by Karaozlan et al. (1989), Nastar and Ayache (1993) and Pentland and Sclaroff (1991). In these frameworks, an object is modelled based on its vibrational modes similar to (34) where \( P_t \) is a vibrational mode rather than a statistical mode.

When the physical characteristics of a tissue are known and several samples from the same tissue are available, one can take advantage of both statistical and physical models to obtain more accurate segmentation, as done by Cootes and Taylor (1995) and Hamarneh et al. (2008) where statistical and vibrational modes of variation are combined into a single objective function.

Schoenemann and Cremers (2007) encoded an elastic shape prior into a segmentation framework by combining the shape matching and segmentation tasks. Given a shape template, they proposed an elastic shape matching term that maps the points of the evolving shape to the template based on two criteria: 1) points of similar curvature should be matched, and 2) a curve piece of the evolving shape should be matched to a piece of the template of equal size. Their method achieves globally optimal solutions.

4.7. Topological prior

Many anatomical objects in medical images have a specific topology that has to be preserved after segmentation in order to obtain plausible results. There are two types of topology specification in the literature: connectivity and genus. Connectivity specification ensures that the segmentation of a single object is connected.\(^3\) The genus information ensures that the final segmentation does not have any void region (if the object is known to be connected) or incorrectly fill void regions when the object is known to have internal holes (Grady, 2012). For example, a doughnut-shape initial segmentation should keep its shape (doughnut) during the segmentation process.

Han et al. (2003) proposed a level set-based method for segmenting objects with topology preservation. Their method is based on the simple point concept from digital topology (Bertrand, 1994). A simple point is one that does not change the topology of the segmentation when it is added or removed from a segmentation. Specifically, the proposed method checks the topological number at each iteration to detect topological changes during the contour evolution. If the segmentation algorithm adds or removes only simple points from an initial segmentation, then the new segmentation will have the same genus as before.

Inspired by Han et al. (2003), Zeng et al. (2008) introduced topology cuts and cast the formulation of Han et al. (2003) in a discrete setting. They showed that the optimization of their energy functional with topology-preservation is NP-hard. In another work, Vicente et al. (2008) proposed an interactive method in the discrete domain to segment objects with topology-preservation. Their algorithm guarantees the connectivity between two designated points. Further, the authors showed that their method can sometime find the global optimum under some conditions. Figure 14 shows examples of encoding topological constraint in segmenting capral bones and cardiac ventricles.

4.8. Moment prior

In most segmentation methods that impose shape prior, deviations of the observed shape from training shapes are usually suppressed by the shape prior imposed. This is undesirable in medical image segmentation where pathological cases occur (i.e. abnormal cases that deviate from the training shapes of healthy organs). Lower-order moment constraints can be an alternative to avoid this limitation.

- **0\(^{th}\) order moment (size/area/volume):** The 0\(^{th}\) order moment corresponds to the size of an object. Ayed et al. (2008) proposed to add the area prior into the level set framework to speed up the curve evolution and to prevent leakage in the final segmentation. Given an image \( I \) and the approximate area value of the targeted object \( |\mathcal{A}| \), their area energy term is defined as:

\[
E_{Area}(x) = \frac{1}{|\mathcal{A}|^2} \left( \int_{\Omega_0} dx - |\mathcal{A}| \right)^2 \int_{\Omega_0} g(I(x)) dx \, , \quad (35)
\]

where \( \Omega_0 \) is the region inside the current segmentation and \( g(.) \) attracts the evolving contour toward the high gradient regions (object boundaries).

- **1\(^{st}\) order moment (location/centroid):** In case of having some rough information about the centroid of the targeted object, this valuable information can be encoded

---

\(^3\)Formally, a segmentation \( S \) is connected if \( \forall x, y \in S, \exists \text{Path}_{xy} \), s.t. if \( z \in \text{Path}_{xy} \), then \( z \in S \).
into a segmentation framework using the 1\textsuperscript{st} order moment as proposed in (Klodt and Cremers, 2011) (see below for more details).

- **Higher-order moment**: Generally, we can impose moment constraints of any order to refine the segmentation and capture fine-scale shape details. Foulonneau et al. (2006) proposed to encode higher-order moments into a level set framework using a local optimization scheme. Recently, Klodt and Cremers (2011) proposed a convex formulation to encode moment constraints. They used the objective function in the form of

\[
E(u) = \int_{\Omega} \rho(x) u(x) dx + \int_{\Omega} g(x)|Du(x)| dx ,
\]

where \( u \in BV : \mathbb{R}^d \rightarrow [0, 1] \) is the labeling function and \( Du \) is the distributional derivative \( (Du(x) = \nabla u(x)) \) for a differentiable \( u \). Relaxing \( u \) to vary between 0 and 1, (36) becomes a convex optimization problem over the convex set \( BV : \mathbb{R}^d \rightarrow [0, 1] \). The global minimizer of the original problem \( (E(u) \) before relaxing \( u \)) is obtained by finding the global minimum of the relaxed energy functional, \( u^* \), and thresholding \( u^* \) by a value \( \mu \in (0, 1) \).

Klodt and Cremers (2011) imposed the 0\textsuperscript{th} order moment (i.e. area constraint in a 2D image) by bounding the area of \( u \) between \( c_1 \) and \( c_2 \) where \( c_1 \leq c_2 \) such that \( u \) lies in the set

\[
C_0 = \left\{ u | c_1 \leq \int_{\Omega} u dx \leq c_2 \right\} .
\]

The exact area prior can be imposed by setting \( c_1 = c_2 \). The 1\textsuperscript{st} moment (i.e. centroid constraint) is imposed by constraining the solution \( u \) to be in the set \( C_1 \) as:

\[
C_1 = \left\{ u | \mu_1 \leq \int_{\Omega} xdx \int_{\Omega} u dx \leq \mu_2 \right\} ,
\]

where \( \mu_1, \mu_2 \in \mathbb{R}^d \). The set \( C_1 \) ensures that the centroid of the segmented object lies between \( \mu_1 \) and \( \mu_2 \). The centroid is fixed when \( \mu_1 = \mu_2 \).

In general, the \( n \)\textsuperscript{th} order moment constraint is imposed as:

\[
C_n = \left\{ u | A_1 \leq \int_{\Omega} (x_1 - \mu_1)^1 \cdots (x_d - \mu_d)^n u dx \int_{\Omega} u dx \leq A_2 \right\} ,
\]

where \( i_1 + \cdots + i_d = n \), \( A_1, A_2 \in \mathbb{R}^{d \times d} \) are symmetric matrices and \( A_1 \leq A_2 \) element wise. Klodt and Cremers (2011) proved that all these sets are convex. In their work, the above constraints (37)-(39) are all hard constraints. Alternatively, all of the aforementioned constraints can be enforced as soft constraints by including them into the energy functional using Lagrange multipliers. Klodt and Cremers (2011) mentioned that, in practice, imposing moments of more than the order of 2 is not very useful as users cannot interpret these moments visually and the improvements are very small.

In the discrete settings, Lim et al. (2011) encode area, centroid and covariance (2\textsuperscript{nd} order constraint) constraints into a graph-based method. While their method does not guarantee a globally optimal solution, their method can impose non-linear combinations of the aforementioned constraints as opposed to (Klodt and Cremers, 2011).

Figure 15 illustrates an example application of using moment constraints in CT segmentation.

### 4.9. Geometrical and region interactions prior

Anatomical objects often consist of multiple regions, each with a unique appearance model, and each has meaningful geometrical relationships or interactions with other regions of the object. Over the past decade, much attention has been given to incorporating geometrical constraints into the segmentation objective function.

In the continuous domain, several methods have been proposed based on coupled surfaces propagation to segment a single object in an image (Zeng et al., 1998; Goldenberg et al., 2002; Paragios, 2002). Vazquez-Reina et al. (2009) defined elastic coupling between multiple level set functions to model ribbon-like partitions. However, their approach was not designed to handle interactions between more than two regions.

Nosrati and Hamarneh (2014) augmented the level set framework with the ability to handle two important and intuitive geometric relationships, containment and exclusion, along with a distance constraint between boundaries of multi-region objects (Figures 16 and 17). Level sets important property of automatically handling topological changes of evolving contours/surfaces enables them to segment spatially recurring objects (e.g. multiple instances of multi-region cells in a large microscopy image) while satisfying the two aforementioned constraints.

Bloch (2005) briefly reviewed the main fuzzy approaches that define spatial relationships including topological relations (i.e. set relationships and adjacency) as well as metrical relations (i.e. distances and directional relative position).

None of the aforementioned methods guarantee a globally optimal solution. In contrast, Wu et al. (2011) proposed a method that yields globally optimal solution for segmenting a region bounded by two coupled terrain-like surfaces. They do so by minimizing the intraclass variance. Despite the global
optimality of their solutions, their method can only segment a single object in an image and is limited to handling objects that can be “unfolded” into two coupled surfaces.

Ukwatta et al. (2012) also proposed a method that is based on coupling two surfaces for carotid adventitia (AB) and lumen-intima (LIB) segmentation. The advantage of their work over previous works is that they optimized their energy functional by means of convex relaxation. However, their method could only segment objects with coupled surfaces. Using the same framework as (Ukwatta et al., 2012), Rajchl et al. (2012) presented a graphical model to segment the myocardium, blood cavities and scar tissue. Their method used seed points as hard constraints to distinguish the background from the myocardium. Nambakhsh et al. (2013) proposed an efficient method for left ventricle (LV) segmentation that iteratively minimizes a convex upper bound energy functional for a coupled surface. Their method implicitly imposes a distance between two surfaces by learning the LV shape. Recently, Nosrati et al. (2013) proposed a convex formulation to incorporate containment and detachment constraints between different regions with a specified minimum distance between their boundaries. Their framework used a single labeling function to encode such constraints while maintaining global optimality. They showed that their convex continuous method is superior to other state-of-the-art methods, including its discrete counterpart, in terms of memory usage and metrication errors.

In the discrete domain, Li et al. (2006) proposed a method to segment “nested objects” by defining distance constraints between the object’s surfaces with respect to a center point. As their formulation employed polar coordinates, their method could only handle star-shaped objects. Two containment and exclusion constraints between distinct regions have been encoded into a graph-cut framework by (Delong and Boykov, 2009) and (Ulén et al., 2013). If only containment constraint is enforced, then both approaches guarantee the global solution. More formally, for a two-region object scenario (region A, B and background), the idea of (Delong and Boykov, 2009) is to create two graphs for A and B, i.e. \( G(V^A, E^A) \) and \( G(V^B, E^B) \). The segmentations of A and B are represented by the binary variables \( x^A \) and \( x^B \), respectively. The geometrical constraints between regions A and B are enforced by adding an additional penalty term \( W^{AB} \) defined in Table 2. This interaction term, \( W \), is implemented in the graph construction by adding inter-layer edges with infinity values as shown in Figure 18(a).

Delong and Boykov (2009) employed what is known as the interaction term \( W \) as follows:

\[
\sum_{pq \in N^{AB}} W^{pq}(f^A_p, f^B_q),
\]

where \( N^{AB} \) is the set of all pixel pairs \((p, q)\) at which region A is assigned some geometric interaction with region B. Table 2 lists energy terms for the region interaction constraints proposed in (Delong and Boykov, 2009). Since the energy terms for containment are submodular, their graph-based method guarantees the globally optimal solution if only containment terms are used. However, the energy for the exclusion constraint is nonsubmodular and thus harder to optimize. In some cases, because exclusion is nonsubmodular everywhere, it is possible to make all these nonsubmodular terms submodular by flipping the meaning of layer B’s variables so that \( f^B_q = 0 \) designates the region’s interior. Nonetheless, there are many useful interaction energy terms that cannot be modeled and optimized efficiently by (Delong and Boykov, 2009) and other approximation like quadratic pseudo-boolean optimization (QPBO) (Kolmogorov and Rother, 2007; Rother et al., 2007) or aff-swap (Boykov et al., 2001) should be used for the optimization of these terms.

4.10. Spatial distance prior

In the literature, works that incorporate spatial distance priors may be categorized as follows:

- **Minimum distance:** In some applications the minimum distance between two structures must be enforced to ensure that sufficient separation between regions exists.
Figure 18: Enforcing containment constraint between objects A and B. Graph constructions used to enforce (a) ‘A contains B’ as proposed by (Delong and Boykov, 2009), and (b) 1-pixel distance between boundaries of regions A and B (shown for a single pixel), respectively.

Table 2: Energy terms for encoding containment and exclusion constraints between regions A and B in (40) (Delong and Boykov, 2009).

|          | A contains B | A excludes B |
|----------|--------------|--------------|
| $f_A^p$  | $f_B^p$      | $W_{AB}^{pq}$|
| 0        | 0            | 0            |
| 0 1      | 1            | ∞            |
| 1 0      | 1            | 0            |
| 1 1      | 1            | ∞            |

to obtain plausible results (e.g. distance between carotid AB and LIB). Examples of methods that employ this constraint include (Zeng et al., 1998; Goldenberg et al., 2002; Paragios, 2002; Nosrati and Hamarneh, 2014; Nosrati et al., 2013) in the continuous settings, and (Wu et al., 2011; Li et al., 2006; Delong and Boykov, 2009; Ulén et al., 2013) in the discrete settings. Looking at (40) for example, Delong and Boykov (Delong and Boykov, 2009) (and similarly, Ulén et al. (Ulén et al., 2013)) enforce the minimum distance between two regions by defining the $N^{AB}$ in (40). Figure 18(b) shows how 1-pixel margin between region boundaries is enforced by (Delong and Boykov, 2009; Ulén et al., 2013).

• **Maximum distance**: In other medical applications, maximum distance between regions is known a priori. For example, in cardiac LV segmentation, maximum distance between LV and its myocardium can be approximated. Enforcing a maximum distance between LV and its myocardium can be approximated. Maximum distance between two boundaries/surfaces is enforced as proposed in (Zeng et al., 1998; Goldenberg et al., 2002; Paragios, 2002; Nosrati and Hamarneh, 2014) in the continuous settings. There is not much work on incorporating maximum distance between region boundaries in discrete settings except for Wu et al. (2011) and Schmidt and Boykov (2012). In (Wu et al., 2011) the maximum distance along with minimum distance prior for segmenting two-region ribbon-like objects can be enforced. To the best of our knowledge, the only work that solely focused on incorporating maximum distance between regions for multi-region object segmentation is the approach proposed by (Schmidt and Boykov, 2012). They modified the framework of (Delong and Boykov, 2009) by adding the Hausdorff distance prior to the MRF-based segmentation framework to impose maximum distance constraints. They showed that incorporating this prior into multi-surface segmentation is NP-hard due to the existence of supermodular energy terms.

• **Attraction/repulsion distance**: In applications like multi-region cell segmentation, distance between regions should be in a specific range. A specific distance between different regions can be maintained by enforcing attraction and repulsion forces between region boundaries as proposed in (Zeng et al., 1998; Goldenberg et al., 2002; Paragios, 2002; Nosrati and Hamarneh, 2014) in the continuous settings. Vazquez-Reina et al. (2009) specifically focused on attraction/repulsion interaction between two boundaries. They defined elastic couplings between level set functions using dynamic force fields to model ribbon-like partitions. Note that none of the above mentioned methods guarantee the globally optimal solution.

In the discrete domain, Wu et al. (Wu et al., 2011) can impose attraction/repulsion force between two surfaces by controlling the minimum and maximum distances between them. Delong and Boykov (2009), and similarly (Ulén et al., 2013; Schmidt and Boykov, 2012), enforced attraction/repulsion between pairs of regions, e.g. A and B, by penalizing the intersection of A and B (i.e. area/volume of $A - B$). Such constraints are encoded in (40) using the penalty terms shown in Table 3. In the contin-

Table 3: Energy terms for encoding containment with attraction/repulsion between A and B regions.

|          | A attracts B |
|----------|--------------|
| $f_A^p$  | $f_B^p$      | $W_{pq}^{AB}$|
| 0        | 0            | 0            |
| 0 1      | 1            | 0            |
| 1 0      | α            | 1            |
| 1 1      | 0            | 0            |
pixels between two regions, (Delong and Boykov, 2009) and (Ulén et al., 2013) need to add $O(n^2)$ extra edges per pixel. Therefore, although these graph-based methods are highly efficient in segmenting images with reasonable size and thickness constraint, they are not that efficient for large distance constraints. On the other hand, the memory usage and time complexity in the continuous methods (e.g. works proposed by (Nosrati and Hamarneh, 2014; Nosrati et al., 2013)) are independent of thickness constraints.

In addition to the above mentioned approaches, methods based on the artificial life framework (deformable organisms) also employ spatial distance constraints to maintain the organism’s structure (Hamarneh et al., 2009; Prasad et al., 2011). In these models, the deformable organism evolves in a restricted way such that the distance between its skeleton and its boundary is restricted to be within a certain range.

4.11. Adjacency prior

Recently, several methods focused on ordering constraints and adjacency relationships on labels for semantic segmentation. As an example, “sheep” and “wolf” are unlikely to be next to each other and label transition from “sheep” to “wolf” should be penalized (Strekalovskiy et al., 2012).

In the discrete settings, Liu et al. (2008) proposed a graph-based method to incorporate label ordering constraints in scene labeling and tiered4 segmentation. They assumed that an image is to be segmented into five parts (“centre”, “left”, “right”, “above” and “bottom”) such that a pixel labeled as “left” cannot be on the right of any pixel labeled as “center”, etc. Liu et al. (2008) encoded such constraints into the pair-wise energy term (regularization), i.e. $\sum_{(p,q)\in\mathcal{N}} V_{pq}(f_p, f_q)$. For example, if pixel $p$ is immediately to the left of $q$, to prohibit $f_p$ = “center” and $f_q$ = “left”, then one defines $V_{pq}("center","left") = \infty$. Generalizing this rule to other cases gives the following settings for $V_{pq}$:

$$
\begin{array}{cccccc}
& L & R & C & T & B \\
L & 0 & \infty & wpq & wpq & wpq \\
R & \infty & 0 & \infty & \infty & \infty \\
C & wpq & 0 & \infty & \infty & \infty \\
T & wpq & wpq & 0 & \infty & \infty \\
B & wpq & wpq & wpq & 0 & \infty \\
\end{array}
$$

$p$ is the left neighbour of $q$

$$
\begin{array}{cccccc}
& L & R & C & T & B \\
L & 0 & \infty & \infty & \infty & \infty \\
R & \infty & 0 & \infty & \infty & \infty \\
C & \infty & 0 & \infty & \infty & \infty \\
T & wpq & wpq & wpq & 0 & \infty \\
B & wpq & wpq & wpq & wpq & \infty \\
\end{array}
$$

$p$ is the top neighbour of $q$

Figure 19 illustrates an example of a tiered labelling. From optimization point of view and according to (Liu et al., 2008), $\alpha$-expansion technique is more likely to get stuck in a local minimum when ordering constraints are used, as $\alpha$-expansion acts on a single label ($\alpha$) at each move. In order to improve on $\alpha$-expansion moves, authors introduced two horizontal and vertical moves and allowed a pixel to have a choice of labels to switch to, as opposed to just a single label $\alpha$. Although their proposed optimization approach leads to better results (compared to $\alpha$-expansion approach), the globally optimal solution is still not guaranteed. Felzenszwalb and Veksler (2010) proposed an efficient dynamic programming algorithm to impose similar constraints as (Liu et al., 2008) but with much less complexity. Their method computes the globally optimal solution in the class of tiered labelings.

In the continuous domain, Strekalovskiy and Cremers (2011) proposed a generalized label ordering constraint which can enforce many complex geometric constraints while maintaining convexity. This method requires that the constraint term obeys the triangle inequality, a requirement that was later relaxed by introducing a convex relaxation method for non-metric priors (Strekalovskiy et al., 2012). To do so, authors enforce non-metric label distances in order to model arbitrary probabilities for label adjacency. The distances between different labels5 operates only directly on neighbouring pixels. This often leads to artificial one pixel-wide regions between labels to allow the transition between labels with very high or infinite distance. For example, both the “wolf” and “sheep” labels can be next to “grass” but they cannot be next to each other (Strekalovskiy et al., 2012). The method proposed in (Strekalovskiy et al., 2012) would create an artificial “grass” region between “wolf” and “sheep” to allow for this transition. Obviously this one-pixel wide distance between “wolf” and “sheep” would not make the sheep any more secured! Generally, a neighbourhood larger than one pixel is needed to avoid these artificial labeling artifacts. Bergbauer et al. (2013) addressed this issue and proposed a morphological proximity prior for semantic image segmentation in a variational framework. The idea is to consider pixels as adjacent if they are within a specified neighbourhood of arbitrary size. Consider two regions $i$ and $j$ and their indicator functions $u_i$ and $u_j$, respectively. To see if $i$ and $j$ are close to each other, the overlap between the dilation of the indicator function $u_i$, denoted by $d_i$, and the indicator function of $u_j$ is computed. The dilation of $u_i$ is formulated as:

$$
d_i(x) = \max_{z \in S} u_i(x + z), \quad \forall x \in \Omega \tag{41}
$$

with a structuring element $S$. For each pair of region $i$ and $j$, a proximity penalty term is defined as:

$$
\sum_{1 \leq i, j < n} \int_{\Omega} A(i,j)d_i(x)u_j(x)d\mathbf{x}, \tag{42}
$$

where $A(i,j)$ indicates the penalty for the co-occurrence of label $j$ in the proximity of label $i$ such that $A(i,i) = 0$. In

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4Tiered labeling problem partitions an input image into multiple horizontal and/or vertical tiers.

5Note that this is not a spatial distance but is a distance between label classes.
4.12 Number of regions/labels

In most segmentation problems, the number of regions is assumed to be known beforehand. However, it is not the case in many applications and predefining a fixed number of labels in these cases often causes over-segmentation.

The intuitive way to handling this problem is to penalize the total number of labels. For the given maximum number of regions/labels (at most $n$ labels), which is available in most applications, Zhu and Yuille (1996) proposed to partition images based on the following energy functional in the continuous domain:

$$\min_{\Omega} \sum_{i=1}^{n} \left\{ \int_{\Omega} \rho(\ell, x) dx + \int_{\partial \Omega} ds \right\} + \gamma M, \quad (43)$$

where $\Omega$ is the region corresponding to label $\ell; \rho(\ell, x)$ is the data term that encodes the model of $\ell$ at pixel $x$; the second term is the regularization term; and $M$ in the third term is the number of non-empty partitions (known as label cost prior). Zhu and Yuille (1996) optimized the above energy functional using a local optimization technique which converges to a local minimum. This approach was later adapted in the level set formulation by (Kadir and Brady, 2003; Ben Ayed and Mitiche, 2008; Brox and Weickert, 2006) that allow region-merging. A convex formulation of such constraint was proposed by Yuan et al. (2012). They enforced the label cost prior into multi label segmentation by solving the following convex optimization problem:

$$\min_{u(x)} \sum_{i=1}^{n} \left\{ \int_{\Omega} u(x)\rho(\ell, x) dx + \int_{\partial \Omega} |\nabla u(x)| dx \right\} + \gamma \sum_{i=1}^{n} \max_{x \in \Omega} u(x)$$

s.t. $\sum_{i=1}^{n} u(x) = 1, \quad u_i(x) \geq 0; \quad \forall x \in \Omega. \quad (44)$

In the discrete domain, Delong et al. (2012a) developed an $\alpha$-expansion method to optimize a general energy functional incorporated with label cost in a graph-based framework.

Along with unary (data) and pairwise (regularization) terms, Delong et al. (2012a) penalized each unique label that appears in the image by introducing the following term:

$$\sum_{l \in L} h_l \cdot \delta_l(f) \quad (45)$$

$$\delta_l(f) = \begin{cases} 1 & \exists p \in \Omega : f_p = l \\ 0 & \text{otherwise} \end{cases}, \quad (46)$$

where $h_l$ is the non-negative label cost of label $l$.

4.13 Motion prior

The segmentation and tracking of moving objects in videos have a wide variety of applications in medical image analysis, e.g., in echocardiography (Dydenko et al., 2006). Paragios and Deriche (1999) used motion prior to constrain the evolution of a level set function by integrating motion estimation and tracking into a level set-based framework. Dydenko et al. (2006) proposed a method to segment and track the cardiac structure in high frame rate echocardiographic images. The motion field is estimated from the level set evolution. Both (Paragios and Deriche, 1999) and (Dydenko et al., 2006) perform motion estimations under the constraint of an affine model. More complex motion prior is used in object tracking. For example, to track the LV in echocardiography, Orderud et al. (2007) employed the Kalman filter, which is an optimal recursive algorithm that uses a series of measurements observed over time to estimate the desired variables (i.e. displacement in motion estimation).

Recently, Nosrati et al. (2014) proposed an efficient technique to segment multiple objects in intra-operative multi-view endoscopic videos based on priors captured from pre-operative data. Their method allows for the inclusion of laparoscopic camera motion model to stabilize the segmentation in the presence of a large occlusion (Figure 20). This feature is especially useful in robotic minimally invasive surgeries as camera motion signals can be easily read using the robot's API and be incorporated into their formulation.

4.14 Model/Atlas

Atlas-based segmentation has also been particularly useful in medical image analysis applications. Works that adopt atlas-based approach include (Gee et al., 1993; Collins et al., 1995;
Collins and Evans, 1997; Iosifescu et al., 1997). An atlas has the ability to encode (non-pathological) spatial relationships between multiple tissues, anatomical structures or organs. In atlas-based image segmentation, the image is non-rigidly deformed and registered with a model or atlas that has been labelled previously. Applying the inverse transformation of the labels to the image space gives the segmentation. However, atlas-based segmentation has so far been restricted to single (albeit multi-part or multi-region) object instance, and does not address spatially recurring objects in the scene. Also, atlases usually are built from datasets of manually segmented images. These manual segmentations may not always be available, and/or cannot be used to define a representative template for a given object in a straightforward manner.

The performance of atlas-based segmentation techniques relies on an accurate registration. Surveying registration methods is beyond the scope of this paper. Interested readers may refer to (Sotiras et al., 2013), (Hill et al., 2001), and Tang and Hamarneh (2013) for more details on image registration.

In the field of computer vision (non-medical), a few techniques used 3D models of objects (more realistic but more complex) to segment 2D images. Prisacariu and Reid (2012) proposed a variational method to segment an object in a 2D image by optimizing a Chan-Vese energy functional with respect to six pose parameters of the object model in 3D. The idea is to transform the object’s model in 3D so that its projection on the 2D image delineates the object of interest. Consider segmenting a single object in an image, Prisacariu and Reid (2012) used the following energy:

\[ E(\phi(x)) = \int_{\Omega} \rho_f(x)H(\phi(x)) + \rho_b(x)(1 - H(\phi(x)))d\Omega, \]  

(47)

where \( \rho_f \) and \( \rho_b \) are two monotonically decreasing functions, measuring matching quality of the image pixels with respect to the foreground and background models, respectively. Instead of optimizing \( E(\phi) \) with respect to the level set function \( \phi \), authors in (Prisacariu and Reid, 2012) proposed to minimize \( E(\phi) \) with respect to the pose parameters \( (\xi_i) \) of the object of interest in 3D space:

\[ \frac{\partial E}{\partial \xi_i} = (\rho_f - \rho_b) \frac{\partial H(\phi)}{\partial \xi_i} = (\rho_f - \rho_b) \delta(\phi) \left[ \frac{\partial \phi}{\partial x} \frac{\partial \phi}{\partial y} \frac{\partial \phi}{\partial z} \right], \]  

(48)

Unlike (Prisacariu and Reid, 2012), Sandhu et al. (2011) derived a gradient flow for the task of non-rigid pose estimation for a single object and used kernel PCA to capture the variance in the space of shapes. Later, Prisacariu et al. (2013), introduced non-rigid pose parameters into the same optimization framework. They capture 3D shape variance by learning non-linear probabilistic low dimensional latent spaces, using the Gaussian process latent variable dimensionality reduction technique. All three aforementioned works (Prisacariu and Reid, 2012; Prisacariu et al., 2013; Sandhu et al., 2011) assume that the camera parameters (for 3D to 2D projection) are given.

Recently, inspired by (Prisacariu and Reid, 2012), Nosrati et al. (2014) proposed a closed-form solution to segment multiple tissues in multi-view endoscopic videos based on pre-operative data. Their method simultaneously estimates the 3D pose of tissues in the pre-operative domain as well as their non-rigid deformations from their pre-operative state. They validated their approach on in vivo surgery data of partial nephrectomy and showed the potential of their method in an augmented reality environment for minimally invasive surgeries. Figure 20 shows an example of segmentation of kidney and tumour in an endoscopic view produced by their method.

5. Summary, discussion, and conclusions

Segmentation techniques are aimed at partitioning (crisply or fuzzily) an image into meaningful parts (two or more). Traditional segmentation approaches (e.g. thresholding, watershed, or region growing) proved incapable of robust and accurate segmentation due to noise, low contrast and complexity of objects in medical images. By incorporating prior knowledge of objects into rigorous optimization-based segmentation formulations, researchers developed more powerful techniques capable of segmenting specific (targeted) objects.

In recent years, several types of prior knowledge have been utilized in a variety of forms (e.g. via user interaction, object shape and appearance, interior and boundary properties, regularization mechanisms, topological and geometrical constraints, moment priors, distance and adjacency constraints, as well as motion and model/atlas-based priors). In this paper, we attempted to provide a comprehensive survey of such image segmentation priors, with a focus on medical imaging applications, including both high-level information as well as the essential technical and mathematical details. We compared different prior in terms of the domain settings (continuous vs. discrete) and the optimizability (e.g. convex or not).

It is important to appreciate that, although incorporating richer prior into an objective function may increase the fidelity of the energy functional (by better modelling the underlying problem), this typically comes at the expense of complicating its optimization (lower optimizability). On the other hand, focusing on optimizability by simplifying the energies might decrease the fidelity of the energy functions. In other words, be wary of segmentation algorithms that always converge to the globally optimal but inaccurate solution, or ones that rely heavily on intricate initialization or meticulously tweaked parameters. Consequently, recent research surveyed has focused on developing methods that increase the optimizability of energy functions (e.g. by proposing convex or submodular energy terms) without sacrificing the fidelity.

In addition to the optimizability-fidelity tradeoff that is impacted by the choice of priors, it is important to observe the runtime and memory efficiency of proposed medical image segmentation algorithms. For example, graph-based approaches may not be very efficient in handling very large images and they often produce artifacts like grid-bias errors (also known as metrication error) due to their discrete nature.

Despite the great advances that have been made in terms of increasing the fidelity and optimizability of various segmenta-
tion energy models, there is still more to be done. We believe that through ongoing research, new methods will be proposed that allow for models that are faithful to the underlying problems, while being globally optimizable, memory- and time-efficient regardless of image size, and are free from any artifacts like metrication error.

In extending prior information in medical image segmentation, there are several directions to explore. One direction may focus on consolidating all of these previously mentioned priors such that a user (or an automatic system) can add one or more of these priors as a module to the segmentation task at hand. Such system is expected to minimize user inputs like manual initialization. Although many efforts have been made to convexify energy terms, many priors (especially when combined together) are non-convex (non-submodular) and hard to optimize. As convex relaxation and convex optimization techniques are becoming popular recently, research emphasis that focuses on convexification of energy functions with as many priors as needed would be an important step toward automatic image segmentation.

In optimization-based segmentation that encodes a set of desired priors, it is important to consider how to combine their respective energy (or objective) terms. The most common approach for dealing with such a multi-objective optimization is to scalarize the energies (via a linear sum of terms). Aside from choosing which priors are relevant and which mathematical formulae encode them, how to learn and set the contribution weight of each term needs to be explored carefully especially when there is not enough training data. When large sets of training data are available, machine learning techniques have been used to discover a good set of weights that adapt to image class, weights that change per image, and spatially adaptive weights.

The priors we reviewed and introduced in this thesis have been specifically and carefully designed to address particular segmentation problem. Another potential complementary approach that is worthy of future exploration is to attempt to learn the priors (not only their weight in the objective function) from available training data.

Future research directions could also focus on combining the hand-crafted features with machine learning techniques in case of availability of training data. For example it makes sense to use expert knowledge when the training data is not available and increase the contribution of machine learning techniques as more data becomes available and/or expert knowledge is harder to collect.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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