A View of Regularized Approaches for Image Segmentation

Laura Antonelli 1,†,‡ 0000-0002-4031-099X, Valentina De Simone 2,‡ 0000-0002-3357-5252 and Daniela di Serafino 3,‡ 0000-0001-8215-0771

1 Institute for High Performance Computing and Networking (ICAR), CNR, Naples, Italy; laura.antonelli@cnr.it
2 University of Campania “Luigi Vanvitelli”, Department of Mathematics and Physics, Caserta, Italy; valentina.desimone@unicampania.it
3 University of Naples Federico II, Department of Mathematics and Applications “R. Caccioppoli”, Naples, Italy; daniela.diserafino@unina.it
* Correspondence: laura.antonelli@cnr.it
† Current address: National Research Council of Italy, via P. Castellino 111, I-80131 Napoli, Italy
‡ All the authors contributed equally to this work.

Abstract: Image segmentation is a central topic in image processing and computer vision and a key issue in many applications, e.g., in medical imaging, microscopy, document analysis and remote sensing. According to the human perception, image segmentation is the process of dividing an image into non-overlapping regions. These regions, which may correspond to different objects, are fundamental for the correct interpretation and classification of the scene represented by the image. The division into regions is not unique, but it depends on the application, i.e., it must be driven by the final goal of the segmentation and hence by the most significant features with respect to that goal. Image segmentation is an inherently ill-posed problem. A classical approach to deal with ill posedness consists in the use of regularization, which allows us to incorporate in the model a-priori information about the solution. In this work we provide a brief overview of regularized mathematical models for image segmentation, considering edge-based and region-based variational models, as well as statistical and machine-learning approaches. We also sketch numerical methods that are applied in computing solutions coming from those techniques.

Keywords: image segmentation; ill-posed problems; regularization; variational models; machine-learning techniques; numerical methods.

MSC: 65D18, 47J30, 65K10, 68T07

1. Introduction and applications

Image segmentation is a fundamental task of image processing, image analysis, image understanding, and pattern recognition. It has a very long history, whose origin may be dated back to about 50 years ago. A seminal paper is [1], where the authors pointed out that an important component of the Stanford Research Institute automation project was a set of programs providing the automaton with a means of interpreting visual data.

While it is possible to accurately represent the information in a real scene by an image, this representation alone does not enable us to highlight specific properties of the scene. Conversely, a description in terms of “natural” elements of the image, such as regions and boundaries of the visualized objects, represented in a uniform manner, provides easy access to useful global information, thus allowing recognition and extraction of specific image features. Thus, to generate a description of specific elements of the image, it is necessary to segment the image into more parts (or segments). Since different types of images (real scenes, synthetic images, medical images, etc. – see Figure 1) may require different partitions to extract significant features, there is no single standard method for image segmentation. On
the other hand, different methods are not equally effective in segmenting a specific type of image, and the criteria to define a successful segmentation depend on the desired goal of the segmentation itself. Thus, the segmentation problem has not a unique result, as shown in Figure 2, where different segmentations of the same image are shown, resulting from different segmentation criteria. Therefore, segmentation is an inherently ill-posed problem and remains a challenging problem in image processing and computer vision, in spite of several decades of research.

Figure 1. Examples of different types of images: (a) natural scene [2], (b) star-forming nursery taken by NASA/ESA Hubble Space Telescope [3], (c) human knee depicted by magnetic resonance imaging [4], (d) multiple projections and sinogram of human brain acquired by Single Photon Emission Tomography [5], (e) handwritten text [6].

With the advances in computer technology and mathematical models, segmentation methods have been refined and improved, maintaining strong relationships with other computer vision methods such as image classification and edge detection, while differing from them by their aims. Despite their strong relationships, those methods address different classes of problems and produce different outputs. Following [7], we can distinguish four main computer vision problems, which are listed next in increasing order of difficulty:

- **image classification**: classify the main object category within an image;
- **object detection**: identify the object category and locate its position using a bounding box, for every known object within an image (edge detection may be considered a subset of this problem);
• **semantic segmentation**: identify the object category of each pixel for every known object within an image;
• **instance segmentation**: identify each object instance of each pixel for every known object within an image.

An illustration of the previous problems is given in Figure 3.

![Image classification](image_classification.png) ![Image detection](image_detection.png) ![Semantic segmentation](semantic_segmentation.png) ![Instance segmentation](instance_segmentation.png)

**Figure 3.** Illustration of the computer vision problems listed in Section 1. The results displayed in (a), (b), (c) and (d) were produced by using Adobe Photoshop.

Image segmentation is used in many application fields, such as biomedicine, remote sensing, public security, transportation, agriculture, environmental analysis, ecology, geology, weather prediction, disaster assessment, and search and rescue. The theoretical and practical results of the increasing research activity on image segmentation promotes their application to new problems, which in turn pose further challenges in the design of mathematical models and numerical solution algorithms. This is also confirmed by the increasing number of documents in the Scopus database that include the word “segmentation” in their titles (see Figure 4). In the following, we outline the use of image segmentation in some application fields. Of course, we are very far from being exhaustive.

![Document by year](documents_by_year.png) ![Documents by subject area](documents_by_subject_area.png)

**Figure 4.** Number of documents indexed in the Scopus database in the last thirty years, which contain the word “segmentation” in the title.

### 1.1. Medical imaging

The segmentation of medical images is commonly used for measuring and visualizing anatomical structures or assessing the functionality of human organs, outlining pathological regions, analyzing biological and metabolic processes, setting therapy plans and image-guided surgery [8,9]. Manual segmentation by experts is not just a tedious and time-consuming process, but also error-prone, especially with the increasing complexity of medical imaging technologies and the huge amount of images to be processed. It is therefore necessary to develop accurate and reliable automatic image segmentation methods, and
also to collect and share image data and segmentation results, in order to better understand complex diseases and to design new therapies (see, e.g., [10] and the references therein). The main medical imaging techniques are listed below together with a very simple description; for further details the reader is referred to [11–15].

- **Radiography (X-Rays)** is a technique using X-rays to produce an image of the internal structure of human organs;
- **Computed Tomography (CT)** refers to a computerized X-ray imaging procedure in which a narrow beam of X-rays is aimed at a patient and quickly rotated around his/her body, producing signals that are processed to generate cross-sectional images (or slices) of human organs to reproduce their three-dimensional structure;
- **Positron Emission Tomography (PET)** provides three-dimensional images describing functional processes of human organs by means of the distribution map of a radiopharmaceutical injected into a patient, emitting pairs of positrons;
- **Single Photon Emission Computed Tomography (SPECT)** is similar to PET, but produces three-dimensional images with lower resolution using single-photon-emitting radiopharmaceuticals;
- **Magnetic Resonance Imaging (MRI)** uses a magnetic field and radio waves to produce structural images of organs and tissues of the human body.

1.2. Microscopy imaging

At a different scale from the previous ones, microscopy images are generally produced using light microscopes [16,17], which provide structural and temporal information about biological and non-biological specimens. In the most widely used light microscopy techniques, the light is transmitted from a source on the opposite side of the specimen to the objective lens. On the contrary, fluorescence microscopy uses the reflected light of the specimen. Electron microscopes are used to produce higher resolution images than light microscopes, providing information that is otherwise inaccessible [18]. There are two main types of electron microscope: Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM), with similar components. Each of them has an electron source that emits an electron stream towards a sample as a source of illumination, and each contains a series of electromagnetic and electrostatic lenses and electron apertures to control the electron beam and capture images. SEM sweeps the electron beam across the sample and records the electrons bouncing back, while TEM works by recording electrons passing through a sample to a detector, providing details as small as individual atoms of the inner structure. Moreover, SEM provides a three-dimensional image of the observed sample, while TEM provides two-dimensional projections of the sample.

Applications of microscopy imaging range from life science to nanotechnology, and from manufacturing processes to environmental monitoring, with very different data and objectives. For example, in biology, the research based on microscopy imaging requires methods for quantitative, unbiased, and reproducible extraction of meaningful measurements to quantify morphological properties as well as to investigate on intra- and inter-cellular dynamics. To address this need, new technologies have been developed, such as microscopy-based screening, sequencing and imaging, with automated analysis (including high-throughput screening [19] and high-content screening [20]), where image segmentation is a fundamental task. Microscopy imaging techniques are also widely used for studying structural and morphological properties of materials at different length scales (from micrometer to angstrom) [21]. Material properties are probed by light microscopy or electron microscopy, and the segmentation aims to detect morphology, texture, microstructure, and chemical composition, and to identify defects in a structure or a mechanical behavior.
1.3. Document image analysis

Document images denote the output of scanning or taking photos of paper documents, as well as video frames where captions are present or pictures of scenes where text is present. Document image analysis is concerned with the transformation of any information present in a document image into an equivalent symbolic representation accessible to computer information processing [22]. In this context, segmentation is a fundamental process to extract information from the image document, such as its basic components (characters, lines, words, pictures). The methods used to achieve this goal generally exploit the differences in the properties of textual and image regions within the document [23,24]. Applications range from historical document validation and signature authentication to document compression and digital document processing [25].

1.4. Remote sensing imaging

Segmentation has been used in remote sensing image processing since the advent of the Landsat-1 satellite.\(^1\) Satellite imaging, as a part of remote sensing, is when satellites scan the Earth using different kinds of sensors to collect electromagnetic radiation reflected from the Earth itself. There exist two main groups of remote sensing systems, classified according to the source of the signal they use to explore, passive and active. Passive remote sensing instruments (e.g., RADAR and LIDAR\(^2\)) rely on the electromagnetic radiation reflected or emitted from the surface of Earth. They are further divided into two groups based on the spectral resolution of the sensors, multispectral and hyperspectral remote sensing [26]. Conversely, active remote sensing instruments (e.g., optical systems) operate with their own electromagnetic energy, transmitted towards Earth’s surface (see [27] for further details). Advances and applications of remote sensing segmentation, e.g., in environmental monitoring (agricultural forestry, rural and urban planning, climate changing, weather forecasting), hydrology (water resources, soil moisture maps, geology), and oceanography (evolution of the ocean basins, monitoring ship traffic, detection oil slicks), among others, can be found in [28–31].

Table 1 lists some research projects related to image segmentation in the application fields previously described.

2. Contribution and outline of this work

We present image segmentation as an ill-posed problem, and discuss widely used models based on regularization approaches, attempting to put them into a coherent mathematical framework. We also show how the key idea of incorporating a-priori information is ubiquitous in regularized models, from well-established ones to newer machine learning approaches, revealing links and similarities between them. Finally, we give a quick overview of some numerical methods used in the application of the various models. Although this is our (partial) view of image segmentation, we believe that it may contribute to better understanding this huge field.

The rest of this paper is organized as follows. In Section 3 we present a mathematical formulation of image segmentation, and in Section 4 we discuss regularized segmentation models, focusing on edge-based, region-based, statistical and machine learning ones. In Section 5 we give a quick overview of numerical techniques that may be used to solve the aforementioned models. Finally, we give some conclusions in Section 6.

---

\(^{1}\) Landsat-1 was the first Earth-observing satellite launched by NASA on July 23, 1972, to study and monitor our planet’s landmasses.

\(^{2}\) RADAR (RAdiation Detection And Ranging) and LIDAR (LIght Detection And Ranging) have the same purpose, i.e., the detection of distance objects, but they differ in the transmitted wavelength used to scan the Earth’s surface.
3. Mathematical formulation of image segmentation

Let \( \mathcal{I} \) be the space of the images defined in a domain \( \Omega \subset \mathbb{R}^d \) \((d \geq 2)\), \( I_0 \in \mathcal{I} \) the observed image, and \( \mathcal{P}_1, \ldots, \mathcal{P}_n \) some propositions representing the features driving the segmentation of \( I_0 \). For example, \( \mathcal{P}_k \) may represent the smoothness or the texture of an image, or may distinguish the objects in the image from the background. Note that \( \mathcal{P}_k \) may be also associated with a function that maps any subset \( A \subset \Omega \) to a logical value, indicating whether the proposition \( \mathcal{P}_k \) is *true* or *false* for all the pixels of \( I_0 \) corresponding to \( A \). Henceforth, we identify \( \mathcal{P}_k \) with that function to simplify the notation.
Table 1. Research projects related to image segmentation in different application fields.

| Project & Repository | Description |
|----------------------|-------------|
| **Medical imaging**  |             |
| BRAINS [32]          | Brain Images of Normal Subjects bank |
| INbreast [33]        | Mammographic databases for breast cancer imaging and study |
| TCIA [34]            | The Cancer Imaging Archive |
| PPMI [35]            | Parkinson Progression Markers Initiative |
| ADNI [36]            | Alzheimer Disease Neuroimaging Initiative |
| OAI [4]              | Osteoarthritis Initiative |
| **Microscopy imaging** |             |
| UCSB Bio [37]        | Segmentation Benchmark dataset of 2D/3D images and sequences |
| BBBC [38]            | Broad Bioimage Benchmark Collection |
| EVICAN [39]          | Expert Visual Cell ANnotation of different cell lines |
| PH² [40]             | Dermoscopic image database for research and benchmarking |
| EMPIAR [41]          | Electron Microscopy Pilot Image ARchive |
| GeoMod2008 [42]      | SEM image dataset for natural and artificial granular materials |
| **Document image analysis** |             |
| Layout Analysis Dataset [43] | Realistic document database (magazines and technical/scientific publications) |
| IMPACT [44]          | Historical documents and books of European libraries |
| REID2019 [45]        | Recognition of Early Indian Printed Documents |
| MNIST [46]           | Database of handwritten digits |
| CEDAR [47]           | Database for handwritten text recognition research |
| **Remote sensing imaging** |             |
| SpaceNet [48]        | Multi-Temporal Urban Development Challenge |
| 95-Cloud [49]        | Scene images from satellite Landsat 8 |
| SEN12MS [50]         | Georeferenced multispectral Sentinel-1/2 imagery |
| LandCoverNet [51]    | Global Land Cover Classification Training Dataset |

Generalizing the definition in [52], the segmentation of \(I_0\) according to the propositions \(P_k, k = 1, \ldots, n\), consists of finding a decomposition of \(\Omega\) into \(m\) connected components \(\Omega_i\), with \(i = 1, \ldots, m\) and \(m \geq n\), such that

1. \(\Omega_i \neq \emptyset\), \(\forall i \in \{1, \ldots, m\}\);
2. \(\Omega_i \cap \Omega_j = \emptyset\), \(\forall i, j \in \{1, \ldots, m\}\) with \(i \neq j\), where \(\Omega_i\) denotes the interior of \(\Omega_i\);
3. \(\bigcup_{i=1}^{m} \Omega_i = \Omega\);
4. \(\forall i \in \{1, \ldots, m\}\) \(\exists! k \in \{1, \ldots, n\}\) such that
   i. \(P_k(I_0|\Omega_i) = true\), where \(P_k(I_0|\Omega_i)\) denotes the restriction of \(P_k\) to \(\Omega_i\),
   ii. \(P_k(I_0|\Omega_j) = false\), \(\forall j \in \{1, \ldots, m\}\) with \(j \neq i\),
   iii. \(P_k(I_0|\Omega_i \cup \Omega_j) = false\), \(\forall j \in \{1, \ldots, m\}\) with \(j \neq i\).

For example, the propositions \(P_1 = \{men\}\), \(P_2 = \{moon\}\) and \(P_3 = \{background\}\) provide the semantic segmentation of Figure 3(a) into the three components shown in Figure 3(c), but if \(P_1\) is changed into \(P'_1 = \{man\}\) the result is the instance segmentation given by the five connected components of Figure 3(d).
Let $\Sigma$ be the space of the possible segmentations of the images in $I$, and $S \in \Sigma$ a particular segmentation of $I_0$. Then $S$ can be also expressed as

$$S = (u^*, I^*),$$

where $u^*$ is a curve that matches the boundaries of the decomposition of $\Omega$, i.e., $u^* = \bigcup_i \partial \Omega_i$, and $I^*$ is a piecewise-smooth function defined on $\Omega$ that approximates $I_0$. In particular, we may assume that the restriction of $I^*$ to any set $\Omega_i$ is differentiable. The segmentation may be also identified directly by using a labeling operator $\Phi$, i.e.

$$S = \Phi(I^*),$$

where

$$\Phi(I(x)) = l_i \text{ if } x \in \Omega_{l_i}$$

$I(x)$ is the value of $I$ associated with $x$, and $l_i \in \mathcal{N} = \{l_1, l_2, \ldots, l_m\}$ is a label.

**4. Regularized segmentation models**

Image segmentation is an ill-posed problem whose solution is highly undetermined or highly ill conditioned or both. Classical approaches for computing a solution of an ill-posed problem require additional information that enforce uniqueness and stability. To this end, regularization methods are widely used. In this case, the solution is generally obtained by minimizing an energy functional $E$ containing a fidelity term $F$ that measures the consistency of the candidate segmentation with the observed image, and a regularization term $R$ that promotes solutions with suitable properties:

$$\begin{aligned}
(I^*, u^*) &= \arg\min_{(I, u)} E(I, u; I_0) = \arg\min_{(I, u)} (F(I, u; I_0) + \lambda R(I, u)).
\end{aligned}$$

(2)

Here $\lambda > 0$ is a regularization parameter that needs careful tuning to suitably balance $F$ and $R$ (see, e.g., [53] and the references therein).

The minimization problem (2) can be solved by writing the Euler-Lagrange equations, which can be derived by integrating by parts the energy functional and using the Gauss theorem along with the fundamental lemma of the calculus of variations. Then a numerical solution can be computed by applying a gradient descent approach, where the descent direction is parameterized by an artificial time, and a discretization by finite differences. A widely used and effective alternative consists in discretizing problem (2) and then solving it by a numerical optimization method. We will come back to these two approaches in Section 5.

Recently, machine learning techniques have been successfully applied to segmentation problems. The key idea is to tune a generic model to a specific solution through learning against sample data (training data). The learning phase extracts prior information to be embedded into the regularization term from a large dataset containing pairs of image and ground-truth labels [54]. Machine learning approaches avoiding the use of a training dataset are also available.

In the next subsections, we provide a few examples of regularized models widely used in image segmentation.

**4.1. Edges-based models**

Edge-based models aim at finding $u^* = \bigcup_i \partial \Omega_i$ by solving the minimization problem (2) with respect to the curve $u$ (in this case, $I$ and $I^*$ are not explicitly considered). Among those models, the Active Contours [55], or Snakes, are the most common ones. Here $u$ in (2)
is a parameterized curve, and the fidelity and regularization terms act as an internal force and an external force, respectively, which move the curve within the image to find the boundaries of the sets \(\Omega_i\). More precisely, the energy functional takes the form

\[
E_{AC}(u) = \int_0^1 g(|\nabla I_0(u(s))|)^2 ds + \lambda \int_0^1 |u'(s)|^2 ds.
\]

(3)

where \(I_0\) is the observed image, \(g\) is an edge-detector function and the curve \(u\) is parametrized by \(s \in [0, 1]\).\(^3\) The first term attracts the curve toward the boundaries, whereas the second one controls its smoothness, and as a result the curve \(u\) changes its shape like a snake.

The evolving curve is driven by surface properties, such as curvature and normal direction, and by image features, such as gray levels and intensity gradient. For example, the mean curvature can be used and in this case the edge-detector function is also responsible for stopping the curve on the edges. For example, \(g\) may be defined as

\[
g(|\nabla I_0|) = \frac{1}{1 + |\nabla (G_{\sigma} * I_0)|^2},
\]

where \(g\) is a positive and decreasing function, \(G_{\sigma}\) is the Gaussian kernel with standard deviation \(\sigma\), and \(*\) denotes the convolution operator. In a Lagrangian approach, an initial curve is evolved by

\[
\frac{\partial u}{\partial t} + L(u) = 0,
\]

(4)

where \(L\) is a differential operator. The simplest evolution is given by \(L(u) = F \cdot N\), where \(N\) is the normal to the curve and \(F\) is a constant that determines the speed of evolution. More generally, the evolution is driven by an external force. For example, in the mean-curvature evolution, \(L(u) = \kappa N\), where \(\kappa\) is the Euclidean curvature of \(u\) [56]. When \(u\) has an explicit representation, it is not easy to deal with topological changes like merge and split, and a re-parametrization of the curve may be required. Therefore, the evolution of the curve \(u\) is commonly described by level-set methods [57], because of their ability to follow topology changes, cusps and corners. In a level set approach, the curve \(u\) is implicitly represented by the zero level set of a function \(\phi(t, x)\), i.e., \(u = \{x \in \Omega : \phi(t, x) = 0\}\). The level set formulations of the simplest evolution and the mean-curvature one read, respectively:

\[
\frac{\partial \phi}{\partial t} = F|\nabla \phi| \quad \text{and} \quad \frac{\partial \phi}{\partial t} = \text{div}(\frac{\nabla \phi}{|\nabla \phi|})|\nabla \phi|.
\]

4.2. Region-based models

Region-based models provide directly the segmentation by means of the image partition \(\{\Omega_i, i = 1, \ldots, n\}\). Region-growing models are among the simplest models falling in this class [58]. Since aggregation criteria based only on gray level measurements may not be sufficient to obtain accurate segmentations, region-growing methods have been merged with variational approaches where the evolution evolves according to the minimization of an energy functional including region-based terms [59].

One of the most popular models was proposed by Mumford and Shah [60]. In this case, the functional \(E\) in (2) takes the form

\[
E(u, \Omega) = \int_{\Omega} (u - u_0)^2 + \lambda |\nabla u|^2 + \mu |\gamma| + \int_{\partial \Omega} |\nabla u|^2.
\]

(5)

With a little abuse of notation we identify the curve \(u\) with its parametrized representation \(u(s)\).
\[ E_{MS}(I, u) = \int_{\Omega} (I - I_0)^2 dx + \lambda \int_{\Omega\setminus u} |\nabla I|^2 dx + \mu \text{len}(u), \]  

where \( \text{len}(u) \) denotes the length of \( u \) and \( \lambda, \mu > 0 \) are regularization parameters. The fidelity term attempts to achieve the minimum distance between \( I_0 \) and the optimal piecewise-smooth approximation \( I \), and the regularization term attempts to reduce the variation of \( I \) within each set \( \Omega_i \) while keeping the curve \( u \) as short as possible. Minimizing (5) in a suitable space provides an optimal pair \( (I^*, u^*) \) representing a simplified description of \( I_0 \) by means a function with bounded variation and a set of edges [60]. Finally, in [61] the Mumford and Shah model is formulated as a deterministic refinement of a probabilistic model for image restoration.

A simplified version of the Mumford-Shah model is its restriction to piecewise-constant functions. The Chan-Vese model [62] is a particular case of that simplified version aimed at obtaining a two-phase segmentation, where the piecewise-constant function assumes only two values. Its functional \( E \) takes the following form:

\[ E_{CV}(I, c_{in}, c_{out}) = \left( \int_{\Omega} H(I)(c_{in} - I_0)^2 dx + \int_{\Omega} (1 - H(I))(c_{out} - I_0)^2 dx \right) \]

\[ + \lambda \int_{\Omega\setminus u} |\nabla H(I)| dx, \]

where \( H \) is the Heaviside function and \( c_{in} \) and \( c_{out} \) are the average values of the intensity in the foreground and background of the image, respectively. The solution \( I^* \) is the best approximation to \( I_0 \) among all the functions that take only two values.

The functional (3) is nonconvex, thus minimization methods may get stuck into local minima and result in unsatisfactory segmentations. Aiming to overcome this drawback, some strategies have been proposed, including the convexification of the functional by taking advantage of its geometric properties. An example is given by the two-phase partitioning model introduced by Chan, Esedoḡlu and Nikolova [63]:

\[ E_{CEN}(I, c_{in}, c_{out}) = \int_{\Omega} \left( (c_{in} - I_0)^2 I + (c_{out} - I_0)^2 (1 - I) \right) dx + \lambda \int_{\Omega\setminus u} |\nabla I| dx \]

with \( 0 \leq I \leq 1 \) and \( c_{in}, c_{out} > 0 \).

4.3. Statistical models

Statistical models usually provide a conditional probability, \( P(S|I_0) \), of a segmentation \( S \in \Sigma \) given the observed image \( I_0 \), and then select the segmentation with the highest probability. In the Maximum a Posteriori (MAP) approach the segmentation is given by

\[ S^* = \arg \max_{S \in \Sigma} P(S|I_0), \]

where the posterior probability \( P(S|I_0) \) can be expressed through the Bayes theorem as

\[ P(S|I_0) \propto P(I_0|S)P(S). \]
Here \( P(S) \) is the prior probability measuring how well \( S \) satisfies certain properties of the given image, and the conditional probability \( P(I_0|S) \) measures the likelihood of \( I_0 \) given \( S \).

Markov Random Field (MRF) models offer a framework to define prior and likelihood by capturing properties of the image such as texture, color, etc. [64]. The segmentation is formulated within an image labeling framework, i.e., \( S = \Phi(I(x)) \), where the problem is reduced to find the labeling which maximizes the posterior probability. Label dependencies are modeled by an MRF; then, using the Hammersley-Clifford theorem, we get the Gibbs distribution

\[
P(S) = \frac{1}{Z} \exp(-U(S)),
\]

where the energy function \( U \) takes the form

\[
U(S) = \sum_{c \in C} V_c(S_c),
\]

\( C \) is the set of cliques of \( S \), \( V_c(S_c) \) is the potential of the clique \( c \in C \) having the label configuration \( S_c \), and \( Z \) is a normalizing constant. The conditional probability \( P(I_0|S) \) is modeled by a Gaussian distribution. Then the original MAP estimation is equivalent to the following energy minimization problem

\[
S^* = \arg \max_{S} P(S|I_0) = \arg \min_{S} U(S).
\]

### 4.4. Machine learning models

Recently, machine learning approaches, and in particular deep learning ones, are being used in solving image segmentation problems, also outperforming the previous approaches. Machine learning approaches do not benefit from prior information on the solution, but “learn” the segmentation from large training datasets.

More in detail, the aim of machine learning methodologies is to define a segmentation model \( f_\theta : I \rightarrow \Sigma \) such that the segmentation of \( I_0 \) can be obtained as \( I^* = f_\theta(I_0) \). The function \( f_\theta \) is usually nonlinear and \( \theta \) is a large set of unknown parameters. The learning phase selects a set of parameters \( \theta \) in order to minimize a loss (or cost) functional that measures the accuracy of the predicted segmentation \( f_\theta(I_0) \). In supervised machine learning, training data are available from databases of manual or annotated segmentations, which provide a large number of pairs \((I_0, I^*) \in X \times Y \subset I \times \Sigma\) (\( X \) is named training set). Thus, \( \theta \) is obtained by minimizing a loss function that often takes the form of a mean square error plus a regularization term:

\[
\theta^* = \arg \min_{\theta} \mathcal{L}(X,Y,\theta) = \arg \min_{\theta} \sum_X \| f_\theta(I_0) - I^* \|^2 + \mathcal{R}_\theta(f_\theta(I_0)).
\]  

In unsupervised machine learning, the training set is not available and the goal is to train \( f_\theta \) to recognize specific patterns or image features in the data. This approach is also referred to as self-supervised learning, because the information is extracted from the data themselves rather than from a set of “predictions” (i.e., given segmentations). Then the fidelity term in (8) takes the form

\[
\sum_I \| f_\theta(I_0) - \Phi(f_\theta(I_0)) \|^2,
\]

where \( \Phi \) is the labeling operator defined in (1).

In order to progressively extract higher-level features from data, machine learning models use a multi-layer structure called neural network, consisting of successive function
compositions. The number of layers is the depth of the model, hence the terminology *deep learning*. A neural network with \( L \) layers is a function

\[
f_\theta : \mathcal{I} \times (H_1 \times \ldots \times H_L) \to \Sigma, \quad f_\theta(I) = (f_L \circ f_{L-1} \circ \ldots \circ f_1)(I),
\]

where \( f_i : \mathbb{R}^{d_{i-1}} \times H_i \to \mathbb{R}^{d_i} \) are the layer functions, each depending on \( \theta_i \), \( d_0 = d \) and \( d_L = n \), with \( n \) equal to the number of features. The adjective “neural” comes from the fact that those networks are loosely inspired by neuroscience.

Neural network structures successfully used in image segmentation are the Multilayer Perceptron (MLP), the Deep Auto-Encoder (DAE) and the Convolutional Neural Network (CNN) [65–68]. Their basic schemes are shown in Figure 5.
MLP is the most simple neural network, composed of multiple layers of perceptrons. A perceptron [69] consists of four main parts: the input values (the image), a matrix of weights and a bias vector, the net sum (matrix-vector multiplication), and an activation function, defined as a nonlinear function that maps values in \((0,1)\) or \((-1,1)\). Popular basic choices for the activation functions are the sigmoid, the hyperbolic tangent, and the rectified linear unit (ReLU) function. The DAE network structure typically consists of \(2L\) layer functions, where the first \(L\) layers act as an encoding function with the input to each layer being of lower dimension than the input to the previous layer, and the remaining \(L\) layers increase the size of their inputs until the final layer produces the same dimension as the image input. The first \(L\) layers are an MLP. Image segmentation by CNN relies on feeding a small area (window) of an image as input to the neural network, which labels the pixels. The CNN scans the image, one area at a time, identifies and extracts features, and uses them to classify the image. A CNN mainly consists of three layers:

- **convolutional layer**: the image is analyzed a few pixels at a time to extract low-level features (edges, color, gradient orientation, etc.);
- **nonlinear layer**: an element-wise activation function creates a feature map with probabilities that each feature belongs to the required class;
- **pooling or downsampling layer**: the amount of features and computation in the network is reduced, hence controlling overfitting.

Among the most well-known CNN architectures successfully used in image segmentation, we mention AlexNet [70], GoogLeNet [71], VGGNet [72], and Fully CNN [73].

**5. Numerical techniques for segmentation models**

The minimization in (2) is usually not trivial and requires appropriate methods, taking into account the specific application. In this section we provide a brief summary of numerical methods that can be applied to segmentation models. We consider two approaches: *first discretize then optimize* and *first optimize then discretize*. In the former, all the quantities in (2) are discretized a priori and then optimization methods are applied to the resulting minimization problem in \(\mathbb{R}^n\). In the latter, we first write first-order optimality conditions for (2), which are generally partial differential equations (PDEs), and then solve those equations by suitable numerical methods, which discretize the equations. Finally, we also sketch some filtering techniques used in image segmentation, although they are not directly applied to the minimization problem (2). This is motivated by their use in some segmentation approaches, such as those based on deep learning.

For the sake of simplicity, here we consider \(d = 2\) and \(S = I\) (i.e., we neglect \(u\) in the segmentation \(S = (I,u)\)). We denote by \(\Omega_{n_x,n_y}\) the discretization of \(\Omega\) consisting of a grid of \(n_x \times n_y\) pixels,

\[
\Omega_{n_x,n_y} = \{(i,j) : i = 1, \ldots, n_x, j = 1, \ldots, n_y\}.
\]
We also identify each pixel with its center and denote by \( S_{i,j} \) the value of \( S \) in \((i,j)\). Finally, we consider the forward and backward difference operators defined as follows:

\[
D^+ x I_{i,j} = I_{i+1,j} - I_{i,j}, \quad D^- x I_{i,j} = I_{i,j} - I_{i-1,j},
\]
\[
D^+ y I_{i,j} = I_{i,j+1} - I_{i,j}, \quad D^- y I_{i,j} = I_{i,j} - I_{i,j-1},
\]

where we assume

\[
I_{i-1,j} = I_{i,j} \quad \text{for} \quad i = 1, \quad I_{i,j-1} = I_{i,j} \quad \text{for} \quad j = 1,
\]
\[
I_{i+1,j} = I_{i,j} \quad \text{for} \quad i = n_x, \quad I_{i,j+1} = I_{i,j} \quad \text{for} \quad j = n_y,
\]
i.e., we define by replication the values of \( I \) with indices outside \( \Omega_{n_x,n_y} \).

5.1. First discretize then optimize

Numerical optimization offers a large variety of methods to compute the segmentation by solving the minimization problem coming from a discretization of (2), possibly subject to constraints that can drive the segmentation towards particular features. The choice of the optimization method depends on the properties of the objective function and/or the constraints.

Roughly speaking, at iteration \( k \), optimization methods for nonlinear problems generate a suitable function \( \tilde{E}(I; I_k) \) that approximates the discretized objective function \( E \) around \( I_k \), and minimize it to obtain the next iterate (see, e.g., [74]). For example, given \( I_k \), the \((k+1)\)-st iteration may be written as

Define \( \tilde{E}(I; I_k) \) that approximates \( E(I; I_0) \)

\[
\tilde{I}_{k+1} = \arg \min_I \tilde{E}(I; I_k)
\]
\[
I_{k+1} = I_k + \alpha_k (\tilde{I}_{k+1} - I_k)
\]

where the step length \( \alpha_k \) satisfies some criterion.

Classical optimization techniques, such as gradient or Newton-type methods [75,76], require regularity assumptions on the objective function (and the constraints, if any). However, many segmentation models are modeled as non-smooth optimization problems. There are two main approaches to deal with non-differentiability: smoothing and non-smoothing [77]. The former formulates the problem as a suitable smooth one and applies the aforementioned classical optimization methods. The latter does not introduce further regularization, and thus uses methods not requiring smoothness. For the purpose of illustration, here we focus on (7), where non-smoothness comes from a discretization of the TV term.

A regularized discrete TV may be obtained as follows:

\[
\int_{\Omega} |\nabla H(I)| \, dx \approx \sum_{i,j} \sqrt{(D^+ x I_{i,j})^2 + (D^+ y I_{i,j})^2 + \epsilon},
\]

where \( \epsilon > 0 \) is “suitably small”, but other regularized versions may be considered, e.g., based on Huber-like functions [78]. In this case, gradient and higher-order methods [75,79–83] can be used efficiently. Another way of introducing regularization consists in splitting the variables into their positive and negative parts (thus doubling the number of unknowns) and introducing new constraints, and then applying first- or second-order methods for smooth problems, such as in [84,85].

Non-smoothing approaches avoid regularization of the non-smooth terms in the optimization problem. This is the case, for example, of methods based on forward-backward
splitting techniques, such as proximal-gradient methods [86,87], and the forward-backward Expectation Maximization (EM) method in [88]. ADMM and split Bregman methods do not use smooth approximations too [53,89–93]. The difficulties associated with the non-differentiability of the TV functional may be also overcome by reformulating the minimization problem as a saddle-point problem and solving it by a primal-dual algorithm such as the Chambolle-Pock one [94,95].

EM algorithms [96] are also widely used to solve statistical models. They are based on the idea of splitting the (negative) log-likelihood into two terms and alternating between the computation of the expectation and its minimization.

Finally, stochastic versions of the previous methods are used in segmentation with deep learning, to limit the computational cost. The idea is to use only random samples of the data at each iteration, to estimate first-order and possibly second-order information according to the loss function, with the aim of significantly reducing the computation and hence the time [97–99].

5.2. First optimize then discretize

Reducing imaging problems to PDEs has many years, because of the availability of a large amount of methods and software for solving PDEs. Over time, some PDE-based methods have been introduced in different ways, such as the Perona-Malik filtering [100], directly based on properties of the PDE [101], and the axiomatic scale space theory [102,103].

In a variational approach, one derives the first-order optimality conditions via smoothing regularized, if it is needed. Let us consider, for example, the level-set formulation of the Chan-Vese model (6), where $I$ is represented by a function $\phi$ such that $\phi(x) = 0$ provides the curve separating two regions of $I$ (when $I = I^*$ the two regions identify the segmentation). Keeping $c_1$ and $c_2$ fixed and writing the Euler-Lagrange equations in a gradient-flow approach, we get

$$\frac{\partial \phi}{\partial t}(t, x) = \delta_\varepsilon(\phi) \left( \lambda \text{div} \left( \frac{\nabla \phi}{|\nabla \phi|} \right) - (c_{in} - I_0)^2 + (c_{out} - I_0)^2 \right) \quad \text{in} \ (0, +\infty) \times \Omega,$$

$$\phi(0, x) = \phi_0(x) \quad \text{in} \ \Omega,$$

$$\frac{\delta_\varepsilon(\phi)}{|\nabla \phi|} \frac{\partial \phi}{\partial N} = 0 \quad \text{on} \ \partial \Omega,$$

where $\delta_\varepsilon$ is a regularized version of the Dirac measure and $N$ is the exterior normal to the boundary $\partial \Omega$ [62].

Finite Difference (FD) schemes [104] are popular methods for the numerical solution of (9). Of course, the discretization used in image segmentation must take into account the nature and the properties of the operators involved in the model. For example, the edge-preserving property is similar to shock-capturing in computational fluid dynamics, and hence finite-difference schemes based on hyperbolic conservation laws can be used [105]. Just to give an example, a level-set equation of the form

$$\frac{\partial \phi}{\partial t} = F|\nabla \phi|,$$

can be solved by using an upwind numerical scheme:

$$\phi^{n+1} = \Psi(\phi^n), \quad \Psi(\phi^n_{i,j}) = \phi^n_{i,j} - \Delta t \left( \max(F, 0) \nabla^+ \phi^n_{i,j} + \min(F, 0) \nabla^- \phi^n_{i,j} \right),$$

where
\[ \nabla^+ \phi_{ij}^n = \left( \max\left( \max(D^{-x}\phi^u_{ij}, 0)^2, -\min(D^{+x}\phi^u_{ij}, 0)^2 \right) \right) + \left( \max\left( \max(D^{-y}\phi^u_{ij}, 0)^2, -\min(D^{+y}\phi^u_{ij}, 0)^2 \right) \right)^{1/2}, \]
\[ \nabla^- \phi_{ij}^n = \left( \max\left( \max(D^{+x}\phi^u_{ij}, 0)^2, -\min(D^{-x}\phi^u_{ij}, 0)^2 \right) \right) + \left( \max\left( \max(D^{+y}\phi^u_{ij}, 0)^2, -\min(D^{-y}\phi^u_{ij}, 0)^2 \right) \right)^{1/2}. \]

5.3. Filters

Discrete filters are often used in image segmentation, e.g., in machine learning approaches. A digital filter is an operator

\[ L : I \in \mathcal{I} \rightarrow \tilde{I} \in \mathcal{I}, \quad \tilde{I}_{ij} = L[I; W_{ij}], \]

where \( W_{ij} \subset \Omega_{n_x,n_y} \). A popular filter in image segmentation is the convolution filter, defined by

\[ \tilde{I}_{ij} = L_{a,b}[I; W_{ij}] = \sum_{s=-a}^{a} \sum_{t=-b}^{b} h_{s,t} I_{i-s,j-t}, \quad (10) \]

with \( a \) and \( b \) positive integers such that \( a \leq \frac{n_x}{2} \) and \( b \leq \frac{n_y}{2} \), \( W_{ij} = \{(s, t) : s = -a, \ldots, a, t = -b, \ldots, b\} \), and \( h_{s,t} \in \mathbb{R} \). The matrix \( H \in \mathbb{R}^{(2a+1) \times (2b+1)} \) such that \( H_{ij} = h_{-a+i,-b+j} \) is called kernel matrix and depends on the features we want extract from the image. Common choices of \( a \) and \( b \) are \( a = b = 3 \) and \( a = b = 5 \).

Edge-detection kernels are frequently used in image segmentation, especially in CNNs. For example, the first layer of a CNN is often responsible for capturing low-level features such as edges, color, and gradient orientation. In general, the choice of \( H \) determines the type of features to be extracted. The kernel matrix

\[ H = \begin{pmatrix} 1 & 0 & -1 \\ 1 & 0 & -1 \\ 1 & 0 & -1 \end{pmatrix} \]

is a vertical edge-detection kernel [106]. Another example is the Sobel operator, used to create an image emphasizing the edges [107]. It allows us to obtain either the gradient amplitude or the gradient direction of the image intensity at each point, by convolving the image with the kernel matrices

\[ H^x_S = \begin{pmatrix} -2 & 0 & -2 \\ -1 & 0 & -1 \end{pmatrix}, \quad H^y_S = \begin{pmatrix} 1 & 2 & -1 \\ 0 & 0 & 0 \\ -1 & -2 & -1 \end{pmatrix}. \]

The gradient magnitude, \( G_{ij} \), and the angle of orientation of the edges, \( \theta_{ij} \), are given by

\[ |G_{ij}| = \sqrt{(H^x_S * I)_{ij}^2 + (H^y_S * I)_{ij}^2}, \quad \theta_{ij} = \arctan((H^y_S * I)_{ij} / (H^x_S * I)_{ij}). \]

A padding process is commonly used to preserve the dimension of the image after the convolution. It consists in adding zeros symmetrically around the border of the image. A pooling layer is usually inserted between two successive convolution layers, which is obtained by applying basic functions, such as max and mean, in a small window.
6. Conclusions

We presented a view of image segmentation, focusing on its mathematical modeling and attempting to put different segmentation models into a coherent framework where regularization plays an important role. We first introduced image segmentation and some of its applications and then discussed edge-based, region-based, statistical and machine learning models. We also provided a summary of numerical methods that are often employed to compute solutions to those models. Our presentation is far from being exhaustive, but nevertheless we think that it can help the reader gain some knowledge in the huge and useful field of image segmentation.

Funding: This work was partially supported by Istituto Nazionale di Alta Matematica - Gruppo Nazionale per il Calcolo Scientifico (INdAM-GNCS), by the Italian Ministry of University and Research under grant no. PON03PE_00060_5, and by the VALERE Program of the University of Campania "L. Vanvitelli".

Acknowledgments: The authors would like to thank G. Trerotola for his technical support.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References
1. Brice, C.R.; Fennema, C.L. Scene analysis using regions. Artificial Intelligence 1970, 1, 205–226. doi:10.1016/0004-3702(70)90008-1.
2. Arbelaez, P.; Maire, M.; Fowlkes, C.; Malik, J. Contour Detection and Hierarchical Image Segmentation. IEEE Transactions on Pattern Analysis and Machine Intelligence 2011, 33, 898–916. doi:10.1109/TPAMI.2010.161.
3. NASA: National Aeronautics and Space Administration. Image of the Day Gallery (16 October 2020). https://www.nasa.gov/.
4. Peterfy, C.; Schneider, E.; Nevitt, M. The Osteoarthritis Initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis and Cartilage 2008, 16, 1433–1441. doi:10.1016/j.joca.2008.06.016.
5. Murli, A.; D’Amore, L.; Carracciuolo, L.; Ceccarelli, M.; Antonelli, L. High performance edge-preserving regularization in 3D SPECT imaging. Parallel Computing 2008, 34, 115–132. doi:10.1016/j.parco.2007.12.004.
6. International Conference on Document Analysis and Recognition. https://scriptnet.iit.demokritos.gr/competitions/~icdar2017htr/.
7. Garcia-Garcia, A.; Orts-Escolano, S.; Oprea, S.; Villena-Martinez, V.; Martinez-Gonzalez, P.; Garcia-Rodriguez, J. A survey on deep learning techniques for image and video semantic segmentation. Applied Soft Computing 2018, 70, 41–65. doi:10.1016/j.asoc.2018.05.018.
8. Suri, J.S.; Setarehdan, S.K.; Singh, S., Eds. Advanced Algorithmic Approaches to Medical Image Segmentation; Springer: Berlin, Heidelberg, 2001. doi:10.1007/978-0-85729-333-6.
9. El-Baz, A.; Jiang, X.; Suri, J. Biomedical Image Segmentation: Advances and Trends; CRC Press, 2016.
10. Antonelli, L.; Guarracino, M.R.; Maddalena, L.; Sangiovanni, M. Integrating imaging and omics data: A review. Biomedical Signal Processing and Control 2019, 52, 264–280. doi:10.1016/j.bspc.2019.04.032.
11. Epstein, C.L. Introduction to the Mathematics of Medical Imaging, 2nd ed.; SIAM, 2007. doi:10.1137/9780898717792.
12. Suetens, P. Fundamentals of Medical Imaging, 2nd ed.; Cambridge University Press, 2009. doi:10.1017/CBO9780511596803.
13. Lancaster, J.; Hasegawa, B. Fundamental Mathematics and Physics of Medical Imaging, 1st ed.; Taylor & Francis Group, 2014. doi:10.1201/b15511.
14. Chappell, M. Principles of Medical Imaging for Engineers, 1 ed.; Springer, 2019. doi:10.1007/978-3-030-30511-6.
15. Murphy, D.; Davidson, M., Fundamentals of Light Microscopy. In Fundamentals of Light Microscopy and Electronic Imaging; John Wiley & Sons, Ltd, 2012; chapter 1, pp. 1–19. doi:10.1007/9781118382905.ch1.
16. Paddock, S.W. Confocal Microscopy, 2 ed.; Humana Press, 2014. doi:10.1007/978-1-60761-847-8.
17. Zaefferer, S. A critical review of orientation microscopy in SEM and TEM. Crystal Research and Technology 2011, 46, 607–628. doi:https://doi.org/10.1002/crat.201100125.
18. Blay, V.; Tolani, B.; Ho, S.P.; Arkin, M.R. High-Throughput Screening: today’s biochemical and cell-based approaches. Drug Discovery Today 2020, 25, 1807–1821. doi:10.1016/j.drudis.2020.07.024.
19. Li, W.; Field, K.G.; Morgan, D. Automated defect analysis in electron microscopic images. npj Computational Materials 2018, 4. doi:10.1038/s41524-018-0093-8.
20. Baird, H.S.; Yamamoto, K.; Bunke, H. Structured Document Image Analysis; Springer: Berlin, Heidelberg, 1992.
23. Eskenazi, S.; Gomez-Kramer, P.; Ogier, J.M. A comprehensive survey of mostly textual document segmentation algorithms since 2008. *Pattern Recognition* 2017, 64, 1–14. doi:10.1016/j.patcog.2016.10.023.

24. Nobile, N.; Suen, C.Y. Text Segmentation for Document Recognition. Handbook of Document Image Processing and Recognition, 2014.

25. Hussain, R.; Raza, A.; Siddiqi, I.; Khurshid, K.; Djeddi, C. A comprehensive survey of handwritten document benchmarks: structure, usage and evaluation. *ELIRASIP Journal on Image and Video Processing* 2015, 3, 46. doi:10.1186/s13640-015-0102-5.

26. Jensen, J. Remote Sensing of the Environment: An Earth Resource Perspective, 2nd ed.; Pearson Education, 2009.

27. Wang, K.; Franklin, S.E.; Guo, X.; Cattet, M. Remote Sensing of Ecology, Biodiversity and Conservation: A Review from the Perspective of Remote Sensing Specialists. *Sensors* 2010, 10, 9647–9667. doi:10.3390/s10110967.

28. Joshi, N.; Baumann, M.; Ehammer, A.; Fensholt, R.; Grogan, K.; Hostert, P.; Jepsen, M.; Kuemmerle, T.; Meyfroidt, P.; Mitchard, E.; et al. A Review of the Application of Optical and Radar Remote Sensing Data Fusion to Land Use Mapping and Monitoring. *Remote Sensing* 2016, 8, 70. doi:10.3390/rs8010070.

29. Hossain, M.D.; Chen, D. Segmentation for Object-Based Image Analysis (OBIA): A review of algorithms and challenges from remote sensing perspective. *ISPRS Journal of Photogrammetry and Remote Sensing* 2019, 150, 115–134. doi:10.1016/j.isprsjprs.2019.02.009.

30. Petropoulos, G.P.; Balzter, H.; Srivastava, P.; Pandey, P.; Bhattacharya, B. Hyperspectral Remote Sensing; Elsevier, 2020. doi:10.1016/C2018-0-01850-2.

31. Booysen, R.; Gloaguen, R.; Lorenz, S.; Zimmermann, R.; Nex, P.A. Geological Remote Sensing. In Encyclopedia of Geology, 2 ed.; Alderton, D.; Elias, S.A., Eds.; Academic Press, 2021; pp. 301–314. doi:10.1016/B978-0-12-409548-9.12127-X.

32. Job, D.E.; Dickie, D.A.; Rodriguez, D.; Robson, A.; Danso, S.; Pernet, C.; Bastin, M.E.; Boardman, J.P.; Murray, A.D.; Waite, G.D.; Staff, R.T.; Deary, I.J.; Shenkin, S.D.; Wardlaw, J.M. A brain imaging repository of normal structural MRI across the life course: Brain Images of Normal Subjects (BRAINS). *Neuroimage* 2017, 144, 299–304. Data Sharing Part II, doi:10.1016/j.neuroimage.2016.01.027.

33. Moreira, I.C.; Amaral, I.; Domingues, I.; Cardoso, A.; Cardoso, M.J.; Cardoso, J.S. InBreast: Toward a Full-field Digital Mammographic Database. *Academic Radiology* 2012, 19, 236–248. doi:10.1016/j.acra.2011.09.014.

34. Clark, K.W.; Vendt, B.A.; Smith, K.E.; Freyman, J.B.; Kirby, J.S.; Moore, S.M.; Phillips, S.R.; Maffitt, D.R.; Pringle, M.; Tarbox, L.; Prior, F.W. The Cancer Imaging Archive (TCIA): Maintaining and Operating a Public Information Repository. *Journal of Digital Imaging* 2013, 26, 1045–1057. doi:10.1007/s10278-013-9622-7.

35. Irwin, D.; Felder, J.; Coffey, C.; Caspall-Garcia, C.; Kang, J.H.; Simuni, T.; Foroud, T.; Toga, A.; Tanner, C.; Kieburtz, K.; Chaahine, L.; Reimer, A.; Hutten, S.; Weintraub, D.; Mollenhauer, B.; Galasko, D.; Siderowf, A.; Marek, K.; Trojanowski, J.; Shaw, L. Evolution of Alzheimer’s Disease Cerebrospinal Fluid Biomarkers in Early Parkinson’s Disease. *Annals of Neurology* 2020, 88, 574–587.

36. Petersen, R.C.; Aisen, P.S.; Beckett, L.A.; Donohue, M.C.; Gamst, A.C.; Harvey, D.J.; Jack, C.R.; Jagust, W.J.; Shaw, L.M.; Toga, A.W.; Trojanowski, J.Q.; Weiner, M.W. Alzheimer’s Disease Neuroimaging Initiative (ADNI). *Neurology* 2010, 74, 201–209. doi:10.1212/WNL.0b013e3181cb3e25.

37. Gelasca, E.D.; Byun, J.; Obara, B.; Manjunath, B. Evaluation and Benchmark for Biological Image Segmentation. IEEE International Conference on Image Processing, 2008.

38. Ljosa, V.; Sokolnicki, K.L.; Carpenter, A.E. Annotated high-throughput microscopy image sets for validation. *Nature Methods* 2012, 9, 637–637. doi:10.1038/nmeth.2083.

39. Schwendy, M.; Unger, R.E.; Parekh, S.H. EVICAN—a balanced dataset for algorithm development in cell and nucleus segmentation. *Bioinformatics* 2020, 36, 3863–3870. doi:10.1093/bioinformatics/btaa225.

40. Mendonça, T.; Ferreira, P.; Marques, J.; Marçal, A.; Rezende, J. PH2 - A dermoscopic image database for research and benchmarking. 2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2013, pp. 5437–5440. doi:10.1109/EMBC.2013.6610779.

41. Iudin, A.; Korir, P.K.; Salavert-Torres, J.; Kleywegt, G.J.; Patwardhan, A. EMPIAR: a public archive for raw electron microscopy image data. *Nature Methods* 2016, 13. doi:10.1038/nmeth.3806.

42. Klinkmüller, M.; Schreurs, G.; Rosenau, M. GeoMod2008 materials benchmark: The axial test dataset. *GFZ Data Services* 2016. doi:10.5880/GFZ.4.1.2016.006.

43. Antonacopoulos, A.; Bridson, D.; Papadopoulos, C.; Pletschacher, S. A Realistic Dataset for Performance Evaluation of Document Layout Analysis. 10th International Conference on Document Analysis and Recognition, 2009. doi:10.1109/ICDAR.2009.271.

44. Papadopoulos, C.; Pletschacher, S.; Clausner, C.; Antonacopoulos, A. The IMPACT Dataset of Historical Document Images. *HIPPoCDAR* 2013. ACM, 2013. doi:10.1145/2501115.2501130.

45. Clausner, C.; Antonacopoulos, A.; Derrick, T.; Pletschacher, S. REID2019 - ICDAR2019 Competition on Recognition of Early Indian Printed Documents. 2019 ICDAR, 2019, pp. 1527–1532. doi:10.1109/ICDAR.2019.00246.

46. Lecun, Y.; Bottou, L.; Bengio, Y.; Haffner, P. Gradient-based learning applied to document recognition. *Proceedings of the IEEE* 1998, 86, 2278–2324. doi:10.1109/5.726791.

47. Hull, J.J. A database for handwritten text recognition research. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 1994, 16, 550–554. doi:10.1109/34.291440.
107. Kanopoulos, N.; Vasanthavada, N.; Baker, R.L. Design of an image edge detection filter using the Sobel operator. *IEEE Journal of Solid-State Circuits* **1988**, *23*, 358–367.