

Margarita Sordo
Sachin Vaidya
Lakhmi C. Jain (Eds.)

Advanced Computational Intelligence Paradigms in Healthcare 3



Springer

Detection and Classification of Microcalcification Clusters in Mammograms using Evolutionary Neural Networks

Rolando R. Hernández-Cisneros and Hugo Terashima-Marín,
and Santiago E. Conant-Pablos

Center for Intelligent Systems, Tecnológico de Monterrey, Campus Monterrey
Ave. Eugenio Garza Sada 2501 Sur, Monterrey, Nuevo León 64849 Mexico
{a00766380, terashima, sconant}@itesm.mx

Summary. Breast cancer is one of the main causes of death in women and early diagnosis is an important means to reduce the mortality rate. The presence of microcalcification clusters are primary indicators of early stages of malignant types of breast cancer and its detection is important to prevent the disease. This chapter presents a procedure for the classification of microcalcification clusters in mammograms using sequential difference of gaussian filters (DoG) and three evolutionary artificial neural networks (EANNs) compared against a feedforward artificial neural network (ANN) trained with backpropagation. It is shown that the use of genetic algorithms (GAs) for finding the optimal weight set for an ANN, finding an adequate initial weight set before starting a backpropagation training algorithm and designing its architecture and tuning its parameters, results mainly in improvements in overall accuracy, sensitivity and specificity of an ANN, compared with other networks trained with simple backpropagation.

7.1 Introduction

Cancer is a term used to refer to a group of diseases where a group of cells of the body grow, change and multiply out of control. Usually, each type of cancer is named after the body part where it originated. When this erratic and uncontrolled proliferation of cells occurs in the breast tissues, it is known as breast cancer.

Breast cancer is the fifth cause of death caused by cancer worldwide, after lung cancer, stomach cancer, liver cancer and colon cancer. During 2005, breast cancer caused approximately 502,000 deaths in the world. Among women, breast cancer is the type of cancer that causes the largest number of deaths worldwide, followed by lung, stomach, colorectal and cervical cancers [71].

The highest survival rates for breast cancer occur when it is detected in its earlier stages, when it usually appears in mammograms as very small specks

of calcium known as microcalcifications. This survival rate decreases as cancer progresses undetected forming a mass or lump, called a tumor (extra tissue formed by rapidly dividing cells). Tumors can be either malignant (cancerous) or benign (non-cancerous). Breast malignant tumors penetrate and destroy healthy breast tissues. Eventually, a group of cells from a tumor may break away and spread to other parts of the body. These groups of cells spreading to another region are called metastases. Survival rates when breast cancer is discovered and begins to be treated in these latest stages are low.

In this chapter, it is presented a procedure for detecting microcalcification clusters in mammograms and classifying them into two classes: benign (usually presence of tiny benign cysts) or malignant (possible presence of early breast cancer). This procedure is mainly based in difference of gaussian (DoG) filters for the detection of suspicious objects in a mammogram, and artificial intelligence techniques like genetic algorithms (GA) and artificial neural networks (ANN) for the classification of such objects into microcalcifications or non-microcalcifications, and later for classifying the detected microcalcification clusters into benign or malignant.

This chapter is organized as follows. In this section, an overview of breast cancer, artificial intelligence techniques and previous work on detection and classification of microcalcifications are presented. In the second section, the proposed procedure along with its theoretical framework are discussed. The third section deals with the experiments and the main results of this work. Finally, in the fourth section, the conclusions are presented.

7.1.1 Breast Cancer

The breast is composed of two main types of tissues: glandular tissues and stromal (supporting) tissues. Glandular tissues include the lobules (milk-producing glands) and the ducts (the milk passages). Stromal tissues consist of all the fatty and fibrous connective tissues of the breast. Additionally, the breast is also made up of lymphatic tissue-immune system tissue whose function is to remove cellular fluids and waste. In Figure 7.1, the stages of breast cancer are shown. Initially, cancer cells are confined to the part of the breast where it originated, and in these stages, it is referred as non-invasive or *in situ*. Ductal carcinoma *in situ* (DCIS), shown in Figure 7.1(b), is the most common form of non-invasive breast cancer (90%). Lobular carcinoma *in situ* (LCIS) is less common and considered a marker for increased breast cancer risk. In time, cancer cells may break from the duct or lobular walls and invade the surrounding fatty and connective tissues of the breast. When this happens, breast cancer is referred as invasive (not necessarily metastatic), as shown in Figure 7.1(c). The previously mentioned types of breast cancer are now referred as infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC) respectively. Finally, at some point they invade through the basement membrane of the duct or lobule and ultimately metastasize to distant organs, as presented in Figure 7.1(d).

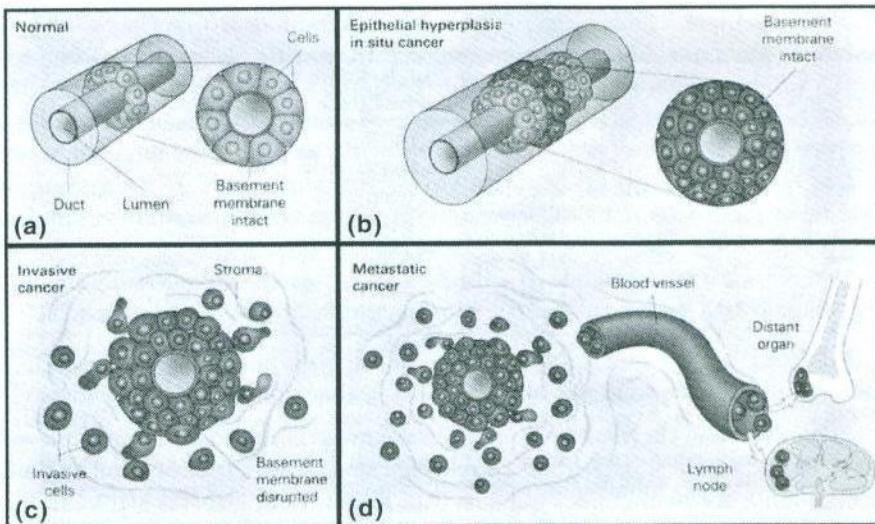


Fig. 7.1. Stages of Breast Cancer [8] (source: <http://carcin.oxfordjournals.org/>)

In order to assess the size and location of a patient's cancer, physicians use a process called staging. Identifying the cancer stage is one of the most important factors in selecting treatment options. There are several tests that may be performed to help to determine the stage of the breast cancer, like clinical breast exams, biopsy, and some imaging tests such as a chest x-ray, mammogram, bone scan, CT scan, and MRI scan. A woman's overall health is evaluated using blood tests, which are also useful to detect if the cancer has metastasized to other parts of the body.

Breast cancer is staged using the TNM system, which is included in the American Joint Committee on Cancer (AJCC) Staging Manual [23]. These stages are:

- Stage 0 - Carcinoma *in situ*.
- Stage I - Tumor (T) does not involve axillary lymph nodes (N).
- Stage IIA - T 2-5 cm, N negative, or T < 2 cm and N positive.
- Stage IIB T > 5 cm, N negative, or T 2-5 cm and N positive (<4 axillary nodes).
- Stage IIIA T > 5 cm, N positive, or T 2-5 cm with 4 or more axillary nodes
- Stage IIIB T has penetrated chest wall or skin, and may have spread to <10 axillary N
- Stage IIIC T has >10 axillary N, 1 or more supraclavicular or infraclavicular N, or internal mammary N.
- Stage IV Distant metastasis (M)

Table 7.1. Five-year Relative Survival Rate for Breast Cancer

Stage	5-year Relative Survival Rate
0	100%
I	100%
IIA	92%
IIB	81%
IIIA	67%
IIIB	54%
IV	20%

The five-year survival rate for breast cancer is calculated based on averages. Each patient's individual tumor characteristics, state of health, genetic background, etc. will impact her survival. In addition, levels of stress, immune function, will to live, and other unmeasurable factors also play a significant role in a patient's survival. The survival rates for each stage of breast cancer are shown in Table 7.1 [1].

It can be deduced that the key to surviving breast cancer is early detection and treatment. In Stage 0, the cancer is "*in situ*" ("in place"), it is contained and has not spread beyond the ducts or lobules where it originated. As shown in Table 7.1, when breast cancer is detected and treated since stage 0, the five-year survival rate is close to 100%. The early detection of breast cancer helps reduce the need for therapeutic treatment and minimizes pain and suffering, allowing women to continue leading happy, productive lives.

Ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) are the two types of breast cancer in stage 0. DCIS is the most frequent of the stage 0 breast cancers, accounting for 80% of the cases, against 20% of the LCIS. DCIS may be detected on mammogram as tiny specks of calcium (known as microcalcifications) 80% of the time. Less commonly DCIS can present itself as a mass with calcifications (15% of the time); and even less likely as a mass without calcifications (less than 5% of the time).

7.1.2 Mammography

Mammography is a special type of x-ray imaging used to create detailed images of the breast. Mammography uses low dose x-ray; high contrast, high-resolution film; and an x-ray system designed specifically for imaging the breasts. Successful treatment of breast cancer depends on early diagnosis. Mammography plays a major role in early detection of breast cancers. According to the US Food and Drug Administration (FDA), mammography can find 85 to 90 percent of breast cancers in women over 50 and can discover a lump up to two years before it can be felt. The benefits of mammography far outweigh the risks and inconvenience.

Mammography can show changes in the breast well before a woman or her physician can feel them. Once a lump is discovered, mammography can be a key in evaluating the lump to determine if it is cancerous or not. If a breast abnormality is found or confirmed with mammography, additional breast imaging tests such as ultrasound (sonography) or a breast biopsy may be performed. A biopsy involves taking a sample(s) of breast tissue and examining it under a microscope to determine whether it contains cancer cells. Many times, mammography or ultrasound is used to help the radiologist or surgeon guide the needle to the correct area in the breast during biopsy.

There are two types of mammography exams, screening and diagnostic:

- Screening mammography is an x-ray examination of the breasts in a woman who is asymptomatic (has no complaints or symptoms of breast cancer). The goal of screening mammography is to detect cancer when it is still too small to be felt by a woman or her physician. Early detection of small breast cancers by screening mammography greatly improves a woman's chances for successful treatment. Screening mammography is recommended every one to two years for women once they reach 40 years of age and every year once they reach 50 years of age. In some instances, physicians may recommend beginning screening mammography before age 40 (i.e. if the woman has a strong family history of breast cancer). Screening mammography is available at a number of clinics and locations. For screening mammography each breast is imaged separately, typically from above (cranial-caudal view, CC) and from an oblique or angled view (mediolateral-oblique, MLO).
- Diagnostic mammography is an x-ray examination of the breast in a woman who either has a breast complaint (for example, a breast lump or nipple discharge is found during self-exam) or has had an abnormality found during screening mammography. Diagnostic mammography is more involved and time-consuming than screening mammography and is used to determine exact size and location of breast abnormalities and to image the surrounding tissue and lymph nodes. Typically, several additional views of the breast are imaged and interpreted during diagnostic mammography, including views from each side (lateromedial, LM: from the outside towards the center and mediolateral view, ML: from the center of the chest out), exaggerated cranial-caudal, magnification views, spot compression, and others. Thus, diagnostic mammography is more expensive than screening mammography. Women with breast implants or a personal history of breast cancer will usually require the additional views used in diagnostic mammography.

Mammography is currently the only exam approved by the U.S. Food and Drug Administration (FDA) to screen for breast cancer in women who do not show any signs or symptoms of the disease. Mammography can detect approximately 85% of breast cancers. If a screening mammography indicates an abnormality, women will most likely be recommended for further breast

imaging (i.e., with spot view mammography, ultrasound or other imaging tests). If further imaging confirms or reveals an abnormality, the woman may be referred for biopsy to determine whether she has breast cancer.

However, while screening mammography can detect most breast cancers, it can miss up to 15% of cancers. These cancers may not be detected on a mammogram film, because of [20]:

- Low differentiation between the appearance of the cancerous tissue compared against the normal parenchymal tissue, specially when the predominant tissue in the breast is very dense.
- Varied morphology of the findings, many of them not related with the cancer.
- Similarities between the morphologies of the findings.
- Possible deficiencies in the mammogram acquisition process.
- Visual fatigue of the radiologist.

The sensitivity may be improved having each mammogram checked by two or more radiologists. It has been proved that double diagnosis improves sensitivity in at most 15% [12,16]. While one radiologist could fail to detect cancer in a small fraction of cases, another one could detect them. Nevertheless, double reading makes the process inefficient from the practical viewpoint, because the small number of specialists available at a given medical institution and their reduced individual productivity. A viable alternative is replacing one of the radiologists by a computer system, giving a second opinion [2,67].

7.1.3 Automatic Detection and Classification of Microcalcifications

Microcalcifications are tiny specks of mineral deposits (calcium), which can be scattered through the mammary gland, or can appear forming clusters. When a specialist detects microcalcifications in a mammogram, he or she observes some features of the particles themselves, and the patterns they present, in order to decide if the specks are of concern and further investigatory techniques or more regular screening are needed. A computer system can be used as a support for the specialists, helping them to make better decisions.

Several authors have tried to solve the problem of automatic detection of microcalcifications in digital mammograms [6,7,11,13,37,38,42,45–47,69,73]. This is not an easy problem to solve, because there are many difficulties caused mainly by the low contrast between microcalcifications and its surroundings, specially when the normal tissue is very dense. Additionally, microcalcifications may be very small, specially in their first stages of formation, making the observation very difficult.

Other authors have dealt with the problem of detecting microcalcification clusters [21,51,54,61,76]. In this case, the objective is to identify individual microcalcifications first, in order to use a clustering algorithm for grouping those microcalcifications.

For the detection of possible microcalcifications in mammograms, several methods have been used, like fractal models [7, 45], adaptive algorithms [68], mathematical morphology [6, 77], image differences [50, 59], artificial neural networks [76], laplacian of gaussians [19], support vector machines [5, 17], etc. For the classification of microcalcifications, methods like artificial neural networks [56], radial basis function (RBF) networks [34], kernel bayes classifiers [10], support vector machines [5], etc. have been applied.

In the following subsections, we describe the methods we use in more detail:

Difference of Gaussians (DoG) Filters

The method selected for this work for the detection of potential microcalcifications was the difference of gaussian filters (DoG). A gaussian filter is obtained from a gaussian distribution. When it is applied to an image, it eliminates high frequency noise, acting as a smoothing filter. A 2-D Gaussian distribution is defined by Equation 7.1:

$$G(x, y) = k e^{-(x^2+y^2)/2\sigma^2} \quad (7.1)$$

where k is the height of the function and σ is the standard deviation.

A DoG filter is a band-pass filter, constructed from two simple gaussian filters. These two smoothing filters must have different variances. By subtracting two images obtained by the application of separate gaussian filters, DoG image containing only a desired range of frequencies is obtained. The DoG is obtained by subtracting two gaussian function, as shown in Equation 7.2.

$$DoG(x, y) = k_1 e^{-(x^2+y^2)/2\sigma_1^2} - k_2 e^{-(x^2+y^2)/2\sigma_2^2} \quad (7.2)$$

The parameters of a DoG must be adapted in order to enhance its detection performance. In other words, the detection capacity of a DoG filter depends of an adequate choice of the standard deviations of each gaussian filter that constitute it. When a DoG filter is applied to an image, a set of regions containing local maxima and minima is obtained. A binarization process allows retrieving only the local maxima, and a segmentation process extracts the regions of interest. DoG filters are adequate for the noise-invariant and size-specific detection of spots, resulting in a DoG image. This DoG image represents the microcalcifications if a thresholding operation is applied to it. We developed a procedure that applies a sequence of Difference of Gaussian Filters, in order to maximize the amount of detected probable microcalcifications (signals) in the mammogram, which are later classified in order to detect if they are real microcalcifications or not. Finally, microcalcification clusters are identified and also classified into malignant and benign.

DoG filters has been used in [14, 48, 52, 58].

Artificial Neural Networks

An artificial neural network (ANN), often just called simply a “neural network” (NN), is a massively parallel distributed processor made up of simple processing units, which has a natural propensity for storing experiential knowledge and making it available for use [28]. The original inspiration for the technique was from examination of the central nervous system and the neurons (and their axons, dendrites and synapses) which constitute one of its most significant information processing elements. It resembles the human brain in two respects:

- Knowledge is acquired through a learning process.
- Synaptic weights are used to store the knowledge.

An ANN has several benefits:

- *Nonlinearity*: A neural network made up of nonlinear neurons has a natural ability to realize (approximate) nonlinear inputoutput functions.
- *Universal approximation*: A neural network can approximate input-output functions (both static and dynamic) to any desired degree of accuracy, given an adequate computational complexity.
- *Adaptivity*: With the synaptic weights of a neural network being adjustable, the network can adapt to its operating environment and track statistical variations.
- *Fault tolerance*: A neural network has the potential to be fault-tolerant, or capable of robust performance, in the sense its performance degrades gradually under adverse operating conditions.
- *Neurobiological analogy*: Neurobiologists look to neural networks as a research tool for the interpretation of neurobiological phenomena. By the same token, engineers look to the human brain for new ideas to solve difficult problems.

According to its architecture, ANNs can be classified in:

- *Single-layer feedforward networks*, which consist of an input layer of source nodes and a single layer of processing units (neurons).
- *Multi-layer feedforward networks*, which contain one or more layers of hidden neurons that are inaccessible from both the input and output sides of the network. In a feedforward network, regardless of its type, signals propagate through the network in a forward direction only.
- *Recurrent networks*, Recurrent networks, which distinguish themselves from feedforward networks in that they contain one or more feedback loops that can be of a local or global kind. The application of feedback provides the basis for short-term memory, and provides a powerful basis for the design of nonlinear dynamical models.

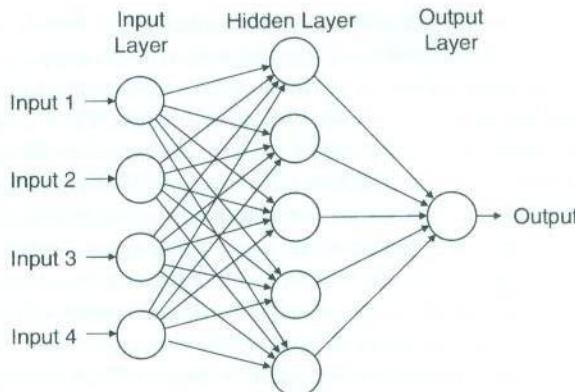


Fig. 7.2. Architecture of a Multi-layer Feedforward Neural Network

In Figure 7.2, the architecture of a multi-layer feedforward neural network (which will be referred as ANN for the remainder of this chapter, for reasons of simplicity) is shown. ANNs are considered to be very powerful classifiers compared to classical algorithms such as the nearest neighbour method. The algorithms used in neural network applications are capable of finding a good classifier based on a limited and in general a small number of training examples. This capability, also referred to as generalization, is of interest from a pattern recognition point of view since a large set of parameters is estimated using a relatively small data set.

Artificial neural networks (ANNs) have been successfully used for classification purposes in medical applications [55, 57, 64], including the classification of microcalcifications in digital mammograms [4, 7, 26, 39, 54, 62, 70, 72, 78]. Unfortunately, for an ANN to be successful in a particular domain, its architecture, training algorithm and the domain variables selected as inputs must be adequately chosen. Designing an ANN architecture is a trial-and-error process; several parameters must be tuned according to the training data when a training algorithm is chosen and, finally, a classification problem could involve too many variables (features), most of them not relevant at all for the classification process itself.

Genetic Algorithms

A Genetic algorithm (GA) is a search algorithm based on the mechanics of natural selection and natural genetics [22]. GAs were developed by John Holland and his colleagues at the university of Michigan in the early 1970s, and became more popular particularly with the publication of his 1975 book [33]. GAs are categorized as global search heuristics, and are a particular class of evolutionary algorithms (also known as evolutionary computation) that use techniques inspired by evolutionary biology such as inheritance, mutation, selection, and crossover (also called recombination).

GAs are implemented as a computer simulation in which a population of abstract representations (called chromosomes, the genotype or the genome) of candidate solutions (called individuals, creatures, or phenotypes) to an optimization problem evolves toward better solutions. Traditionally, solutions are represented in binary as strings of 0s and 1s, but other encodings are also possible. The evolution usually starts from a population of randomly generated individuals and happens in generations. In each generation, the fitness of every individual in the population is evaluated, multiple individuals are stochastically selected from the current population (based on their fitness), and modified (recombined and possibly randomly mutated) to form a new population. The new population is then used in the next iteration of the algorithm. Commonly, the algorithm terminates when either a maximum number of generations has been produced, or a satisfactory fitness level has been reached for the population. If the algorithm has terminated due to a maximum number of generations, a satisfactory solution may or may not have been reached. GAs have been applied successfully in many field, like biogenetics, computer science, engineering, economics, chemistry, manufacturing, mathematics, physics, etc.

A typical GA requires two things to be defined:

- a genetic representation of the solution domain,
- a fitness function to evaluate the solution domain.

A solution is commonly represented as an array of bits. Arrays of other types (integer, real numbers, etc.) and structures can be used in essentially the same way. The main property that makes these genetic representations convenient is that their parts are easily aligned due to their fixed size, that facilitates simple crossover operation. Variable length representations may also be used, but crossover implementation is more complex in this case. The fitness function is defined over the genetic representation and measures the quality of the represented solution.

The pseudo-code of a simple GA is the following:

1. Choose initial population
2. Evaluate the fitness of each individual in the population
3. Repeat
4. a) Select best-ranking individuals to reproduce
- b) Breed new generation through crossover and mutation (genetic operations) and give birth to offspring
- c) Evaluate the individual fitnesses of the offspring
- d) Replace worst ranked part of population with offspring
5. Until <terminating condition>

The population size depends on the nature of the problem, but typically contains several hundreds or thousands of possible solutions. Traditionally, the initial population is generated randomly, covering the entire range of possible

solutions (the search space). Occasionally, the solutions may be “seeded” in areas where optimal solutions are likely to be found. During each successive generation, a proportion of the existing population is selected to breed a new generation. Individual solutions are selected through a fitness-based process, where fitter solutions (as measured by a fitness function) are typically more likely to be selected. Popular and well-studied selection methods include roulette wheel selection and tournament selection.

The next step is to generate a second generation population of solutions from those selected through genetic operators: crossover (also called recombination), and/or mutation. For each new solution to be produced, a pair of “parent” solutions is selected for breeding from the pool selected previously. By producing a “child” solution using the above methods of crossover and mutation, a new solution is created which typically shares many of the characteristics of its “parents”. New parents are selected for each child, and the process continues until a new population of solutions of appropriate size is generated. These processes ultimately result in the next generation population of chromosomes that is different from the initial generation. Generally the average fitness will have increased by this procedure for the population, since only the best organisms from the first generation are selected for breeding, along with a small proportion of less fit solutions.

This generational process is repeated until a termination condition has been reached. Common terminating conditions are

- A solution is found that satisfies minimum criteria
- A fixed number of generations is reached
- The allocated budget (computation time/money) is reached
- The highest ranking solution’s fitness is reaching or has reached a plateau such that successive iterations no longer produce better results
- Manual inspection
- Combinations of the above.

Evolutionary Neural Networks

Genetic algorithms (GAs) may be used to address the inherent problems presented by the ANNs mentioned previously, helping to obtain more accurate ANNs with better generalization abilities. Evolutionary artificial neural networks (EANNs) refer to a special class of ANNs in which evolution is another fundamental form of adaptation in addition to learning [74].

A distinctive feature of EANNs is their adaptability to a dynamic environment. EANNs are able to adapt to an environment as well as changes in the environment. These two forms of adaptation, evolution and learning in EANNs, make their adaptation to a dynamic environment much more effective and efficient. In a broader sense, EANNs can be regarded as a general framework for adaptive systems, systems that can change their architectures and learning rules appropriately without human intervention.

GAs can interact with ANNs at roughly three different levels: connection weights, architectures, and learning rules. The evolution of connection weights introduces an adaptive and global approach to training, especially where gradient-based training algorithms often experience great difficulties. The evolution of architectures enables ANNs to adapt their topologies to different tasks without human intervention and thus provides an approach to automatic ANN design as both ANN connection weights and structures can be evolved. The evolution of learning rules can be regarded as a process of “learning to learn” in ANNs where the adaptation of learning rules is achieved through evolution. It can also be regarded as an adaptive process of automatic discovery of novel learning rules [75].

EANNs that evolve connection weights overcome the shortcomings of the common gradient-descent-based training algorithms, by formulating the training process as the evolution of connection weights in the environment determined by the architecture and the learning task. GAs can then be used effectively in the evolution to find a near-optimal set of connection weights globally without computing gradient information. The fitness of an ANN can be defined according to different needs. Two important factors which commonly appear in the fitness (or error) function are the error between target and actual outputs and the complexity of the ANN. Unlike the case in gradient-descent-based training algorithms, fitness (or error) function does not have to be differentiable or even continuous since GAs do not depend on gradient information. Because GAs can treat large, complex, non-differentiable, and multimodal spaces, considerable research and application has been conducted on the evolution of connection weights.

In the evolution of connection weights, the architecture of the EANN is assumed to be predefined and fixed. The architecture design of an ANN is crucial for its successful application, because the architecture has a significant impact in the ANN performance. Traditionally, ANN architecture design is a job for human experts, who define the topology of the ANN based on their experience and a trial-and-error process. There is no a systematic way to design a near-optimal architecture for a given task. Design of the optimal architecture for an ANN has been formulated as a search problem in the architecture space where each point represents an architecture. Given some performance (optimality) criteria (lowest training error, lowest network complexity, etc.) about architectures, the performance level of all architectures forms a discrete surface in the space. The optimal architecture design is equivalent to finding the highest point on this surface, and GAs are adequate for this task.

Exhaustive reviews about EANNs have been presented by Yao [75] and Balakrishnan and Honavar [3]. More specifically, Fogel et al. [18] presented one of the first works about EANNs for screening features from mammograms. In this chapter, we present an automated procedure for feature extraction and training data set construction for training an ANN is proposed. It is also described the use of GAs for 1) finding the optimal weight set for an ANN, 2) finding an adequate initial weight set for an ANN before starting

a backpropagation training algorithm and 3) designing the architecture and tuning some parameters of an ANN. All of these methods are applied to the classification of microcalcifications and microcalcification clusters in digital mammograms, expecting to improve the accuracy of an ordinary feedforward ANN performing this task. Some of our previous work on this subject is presented in [29–32, 53].

7.2 Methodology

The mammograms used in this project were provided by the Mammographic Image Analysis Society (MIAS) [66]. The MIAS database contains 322 images with resolutions of 50 microns/pixel and 200 microns/pixel. Only 118 in the database contain some abnormality (66 are benign and 52 are malignant) and the other 204 are diagnosed as normal. The abnormalities found in these mammograms are microcalcifications (25 cases), circumscribed masses (20 cases), spiculated masses (21 cases), ill-defined masses (15 cases), architectural distortions (20 cases) and asymmetries (17 cases). In this work, the images with a resolution of 200 microns/pixel were used. The data has been reviewed by a consultant radiologist and all the abnormalities have been identified and marked. The truth data consists of the location of the abnormality and the radius of a circle which encloses it. From the 25 images containing microcalcifications, 13 cases are diagnosed as malignant and 12 as benign. Several related works have used this same database [35, 44], some of them specifically for detecting individual microcalcifications [24, 41, 49, 60] and some others for detecting clusters [15, 27, 43, 65].

The general procedure receives a digital mammogram as an input, and it is conformed by five stages: pre-processing, detection of potential microcalcifications (signals), classification of signals into real microcalcifications, detection of microcalcification clusters and classification of microcalcification clusters into benign and malignant. The diagram of the proposed procedure is shown in Figure 7.3. As end-products of this process, we obtain two ANNs for classifying microcalcifications and microcalcifications clusters respectively, which in this case, are products of the evolutionary approaches that are proposed.

7.2.1 Pre-processing

During the mammogram acquisition process, and during the digitalization of the X-ray plaque, some noise can be added unintentionally to the images. Furthermore, only about 40% of each mammogram corresponds to the actual mammary gland. The remainder of the image is the background, that may also contain marks or labels that identify the mammogram, not relevant to the computer system. The pre-processing stage has the aim of eliminating those elements in the images that could interfere in the process of identifying microcalcifications. A secondary goal is to reduce the work area only to the relevant region that exactly contains the breast.

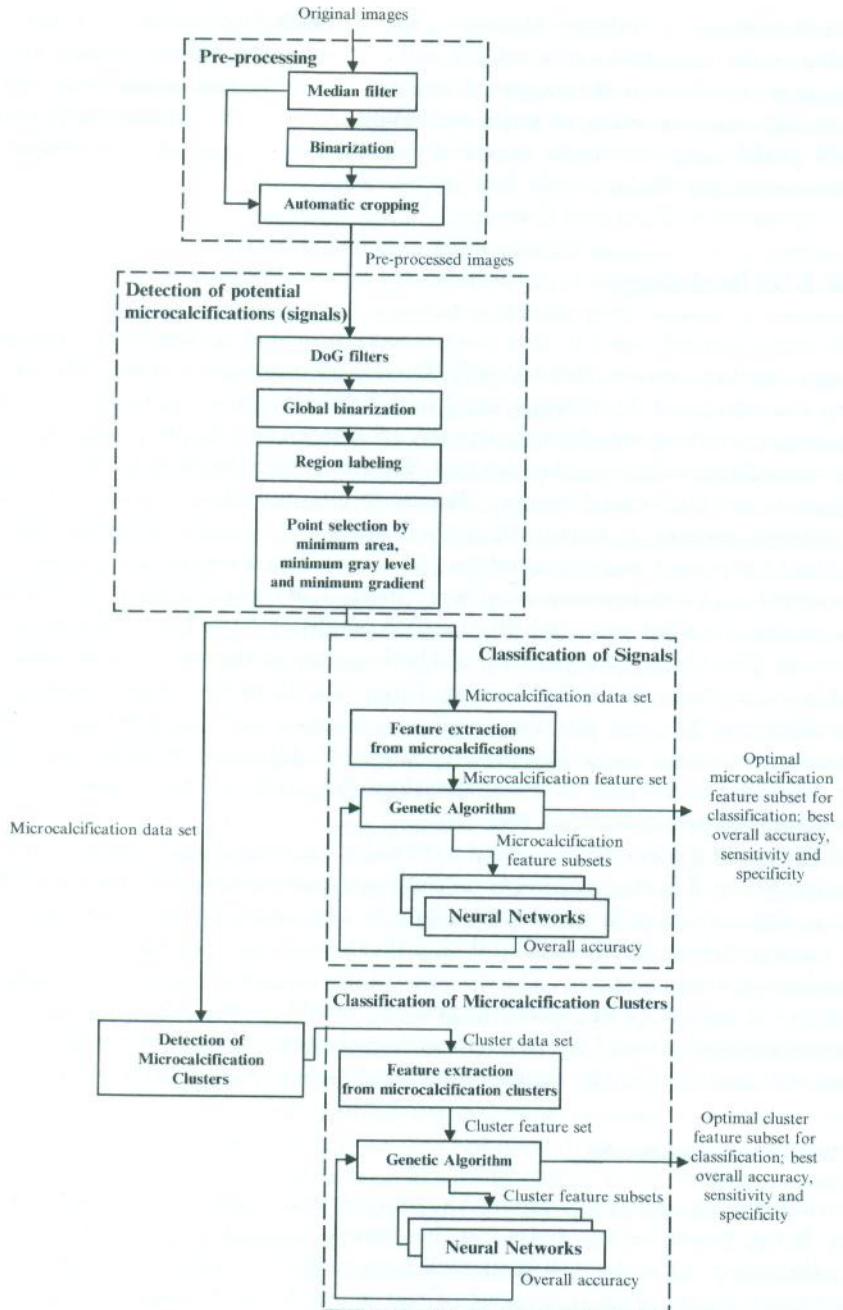


Fig. 7.3. Diagram of the proposed procedure

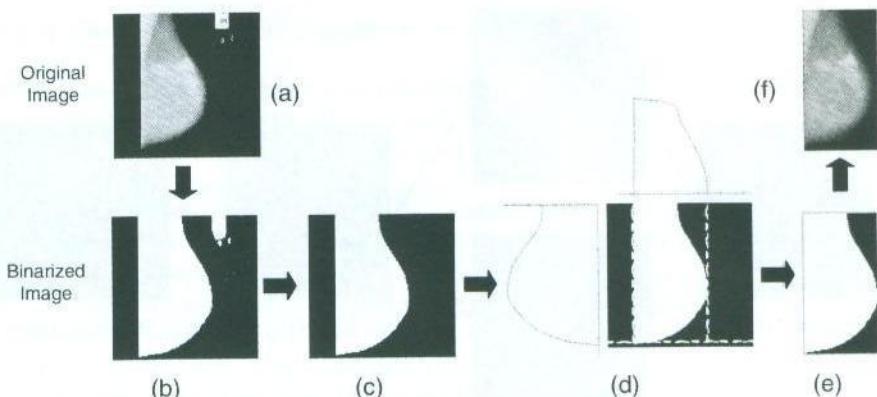


Fig. 7.4. The Pre-processing Stage: (a) original image, (b) binarized image, (c) binarized image without isolated regions, (d) determination of the boundaries for trimming, (e) trimmed binarized image and (f) trimmed original image

The procedure receives the original images as input. First, a median filter is applied in order to eliminate the background noise, keeping the significant features of the images. A median filter is a non-linear filter frequently used to eliminate high frequency noise without deleting significant features of the image. A 3×3 mask was used, centering it in each pixel of the image, replacing the value of the central pixel with the median of the surrounding nine pixels covered by the mask. The size of this mask was chosen empirically, trying to avoid the loss of local details.

Next, binary images are created from each filtered image. The purpose of the binary images is to help an automatic cropping procedure to delete the background marks and the isolated regions, so the image will contain only the region of interest. The cropping procedure first eliminates isolated elements that are not connected with the group of pixels corresponding to the breast, and then makes adequate vertical and horizontal cuts based on the sums of pixels by rows and columns in the binary image. Figure 7.4 depicts the pre-processing stage.

7.2.2 Detection of Potential Microcalcification (Signals)

The main objective of this stage is to detect the mass centers of the potential microcalcifications in the image (signals). The optimized difference of two gaussian filters (DoG) is used for enhancing those regions containing bright points. The resultant image after applying a DoG filter is globally binarized, using an empirically determined threshold. In Figure 7.5, an example of the application of a DoG filter is shown. A region-labeling algorithm allows the identification of each one of the points (defined as high-contrast regions detected after the application of the DoG filters, that cannot be considered microcalcifications yet). Then, a segmentation algorithm extracts small 9×9

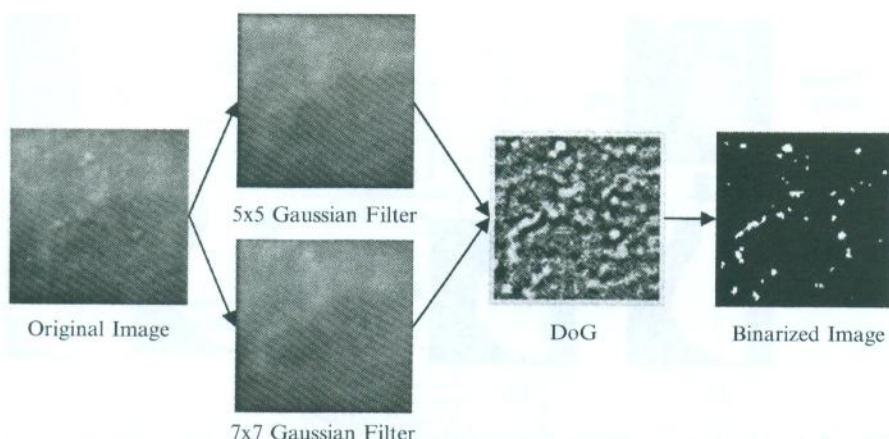


Fig. 7.5. Example of the application of a DoG filter (5×5 , 7×7)

windows each, containing the region of interest whose centroid corresponds to the centroid of each point. In order to detect the greater possible amount of points, six gaussian filters of sizes 5×5 , 7×7 , 9×9 , 11×11 , 13×13 and 15×15 are combined, two at a time, to construct 15 DoG filters that are applied sequentially. Each one of the 15 DoG filters was applied 51 times, varying the binarization threshold in the interval $[0, 5]$ by increments of 0.1. The points obtained by applying each filter are added to the points obtained by the previous one, deleting the repeated points. The same procedure is repeated with the points obtained by the remaining DoG filters. All of these points are passed later to three selection procedures.

These three selection methods are applied in order to transform a point into a signal (potential microcalcification). The first method performs selection according to the object area, choosing only the points with an area between a predefined minimum and a maximum. For this work, a minimum area of 1 pixel (0.0314 mm^2) and a maximum of 77 pixels (3.08 mm^2) were considered. The second method performs selection according to the gray level of the points. Studying the mean gray levels of pixels surrounding real identified microcalcifications, it was found they have values in the interval [102, 237] with a mean of 164. For this study, we set the minimum gray level for points to be selected to 100. Finally, the third selection method uses the gray gradient (or absolute contrast, the difference between the mean gray level of the point and the mean gray level of the background). Again, studying the mean gray gradient of point surrounding real identified microcalcifications, it was found they have values in the interval [3, 56] with a mean of 9.66. For this study, we set the minimum gray gradient for points to be selected to 3, the minimum value of the interval. The result of these three selection processes is a list of signals (potential microcalcifications) represented by their centroids.

7.2.3 Classification of Signals into Real Microcalcifications

The objective of this stage is to identify if an obtained signal corresponds to an individual microcalcification or not. A set of features are extracted from the signal, related to their contrast and shape. From each signal, 47 features are extracted, related to:

- *Signal contrast*: Features related to the gray level of the pixels that are part of the signal (7 features).
- *Background contrast*: Features related to the gray level of the pixels that form the background in the window containing the signal (7 features).
- *Relative contrast*: Features that relate the mean gray level of the signal with the mean gray level of the background (3 features).
- *Shape features*: Features that describe the shape of the signal (20 features).
- *Contour sequence moments*: Moments of shape, mean and standard deviation extracted from the distance to the signal centroid (6 features).
- *Invariant geometric moments*: The first four invariants of Hu [36] (4 features).

A summary of the features extracted from the signals is presented in Table 7.2.

There is not an a priori criterion to determine what features should be used for classification purposes, so the features pass through two feature selection processes [40]: the first one attempts to delete the features that present

Table 7.2. Summary of features extracted from the signals (potential microcalcifications)

Signal contrast	Maximum gray level, minimum gray level, median gray level, mean gray level, standard deviation of the gray level, gray level skewness, gray level kurtosis.
Background contrast	Background maximum gray level, background minimum gray level, background median gray level, background mean gray level, standard deviation of the background gray level, background gray level skewness, background gray level kurtosis.
Relative contrast	Absolute contrast, relative contrast, proportional contrast.
Shape features	Area, convex area, background area, perimeter, maximum diameter, minimum diameter, equivalent circular diameter, fiber length, fiber width, curl, circularity, roundness, elongation1, elongation2, eccentricity, aspect ratio, compactness1, compactness2, compactness3, solidity.
Contour sequence moments	CSM1, CSM2, CSM3, CSM4, mean radii, standard deviation of radii.
Invariant geometric moments	IM1, IM2, IM3, IM4.

high correlation with other features, and the second one uses a derivation of the forward sequential search algorithm, which is a sub-optimal search algorithm. The algorithm decides what feature must be added depending of the information gain that it provides, finally resulting in a subset of features that minimize the error of the classifier (which in this case was a conventional feed-forward ANN). After these processes were applied, only three features were selected and used for classification: absolute contrast (the difference between the mean gray levels of the signal and its background), standard deviation of the gray level of the pixels that form the signal and the third moment of contour sequence. Moments of contour sequence are calculated using the signal centroid and the pixels in its perimeter, and are invariant to translation, rotation and scale transformations [25].

In order to process signals and accurately classify the real microcalcifications, we decided to use ANNs as classifiers. Because of the problems with ANNs already mentioned, we decided also to use GAs for evolving populations of ANNs, in three different ways, some of them suggested by Cantú-Paz and Kamath [9]. The first approach uses GAs for searching the optimal set of weights of the ANN. In this approach, the GA is used only for searching the weights, the architecture is fixed prior to the experiment. The second approach is very similar to the previous one, but instead of evaluating the network immediately after the initial weight set which is represented in each chromosome of the GA, is assigned, a backpropagation training starts from this initial weight set, hoping to reach an optimum quickly [63]. The last approach is not concerned with evolving weights. Instead, a GA is used to evolve a part of the architecture and other features of the ANN. The number of nodes in the hidden layer is very important parameter, because too few or to many nodes can affect the learning and generalization capabilities of the ANN. In this case, each chromosome encodes the learning rate, a lower and upper limits for the weights before starting the backpropagation training, and the number of nodes of the hidden layer.

At the end of this stage, we obtain three ready-to-use ANNs, each one taken from the last generation of the GAs used in each one of the approaches. These ANNs have the best performances in terms of overall accuracy (fraction of well classified objects, including microcalcifications and other elements in the image that are not microcalcifications).

7.2.4 Detection of Microcalcification Clusters

During this stage, the microcalcification clusters are identified. The detection and posterior consideration of every microcalcification cluster in the images may produce better results in a subsequent classification process, as we showed in [53].

Some authors define a microcalcification cluster as a group of three or more microcalcifications occupying a space lesser than 1 cm^2 [21, 54, 61], while others state that it is a group of two or more microcalcifications [76]. In this

work, only the first definition is considered. We consider that every cluster fits inside a circle that contains a square with an area of 1 cm², that is, a circle with a radius of 0.7 cm. This radius, translated to pixels considering the resolution of 200 microns per pixel, is about 100 pixels in length.

This procedure receives a list of the microcalcifications obtained in the previous stage as input, and then produces a list of cluster features extracted and selected from each cluster. An algorithm for locating microcalcification cluster regions where the quantity of microcalcifications per cm² (density) is higher, was developed. This algorithm keeps adding microcalcifications to their closest clusters at a reasonable distance until there are no more microcalcifications left or if the remaining ones are too distant for being considered as part of a cluster. Every detected cluster is then labeled.

7.2.5 Classification of Microcalcification Clusters into Benign and Malignant

This stage has the objective of classifying each cluster in one of two classes: benign or malignant. This information is provided by the MIAS database.

From every microcalcification cluster detected in the mammograms in the previous stage, a cluster feature set is extracted. The feature set is constituted by 30 features, related to:

- *Cluster shape*: Features related to the convex polygon that contains all the microcalcifications of a cluster, and from the radii that connect each microcalcification to the cluster centroid (14 features).
- *Microcalcification area*: Features obtained from the area of the microcalcifications in the cluster (6 features).
- *Microcalcification contrast*: Features obtained from the mean gray level of the microcalcifications in the cluster (10 features).

These features are shown in Table 7.3.

The same two feature selection procedures mentioned earlier are also performed in this stage. Only three cluster features were selected for the classification process: minimum diameter, minimum radius and mean radius of the clusters. The minimum diameter is the maximum distance that can exist between two microcalcifications within a cluster in such a way that the line connecting them is perpendicular to the maximum diameter, defined as the maximum distance between two microcalcifications in a cluster. The minimum radius is the shortest of the radii connecting each microcalcification to the centroid of the cluster and the mean radius is the mean of these radii.

In order to process microcalcification clusters and accurately classify them into benign or malignant, we decided again to use ANNs as classifiers. We use GAs for evolving populations of ANNs, in the same three different approaches we used before for classifying signals. The first approach uses GAs for searching the optimal set of weights of the ANN. The second approach uses a GA

Table 7.3. Summary of features extracted from the microcalcification clusters

Cluster shape	Number of calcifications, convex perimeter, convex area, compactness, microcalcification density, total radius, maximum radius, minimum radius, mean radius, standard deviation of radii, maximum diameter, minimum diameter, mean of the distances between microcalcifications, standard deviation of the distances between microcalcifications.
Microcalcification Area	Total area of microcalcifications, mean area of microcalcifications, standard deviation of the area of microcalcifications, maximum area of the microcalcifications, minimum area of the microcalcifications, relative area.
Microcalcification Contrast	Total gray mean level of microcalcifications, mean of the mean gray levels of microcalcifications, standard deviation of the mean gray levels of microcalcifications, maximum mean gray level of microcalcifications, minimum mean gray level of microcalcifications, total absolute contrast, mean absolute contrast, standard deviation of the absolute contrast, maximum absolute contrast, minimum absolute contrast.

for defining initial weight sets, from which a backpropagation training algorithm is started, hoping to reach an optimum quickly. The third approach uses a GA for evolving the architecture and other features of the ANN as it was shown in a previous stage, when signals were classified. Again, each chromosome encodes the learning rate, a lower and upper limits for the weights before starting the backpropagation training, and the number of nodes of the hidden layer. For comparison, a conventional feedforward ANN is used also.

At the end of this stage, we obtain three ready-to-use ANNs, each one taken from the last generation of the GAs used in each of the approaches. These ANNs have the best performances in terms of overall accuracy (fraction of well classified clusters).

7.3 Experiments and Results

In this section, the experiments performed and the results obtained in every phase of the process are presented and discussed in detail.

7.3.1 From Pre-processing to Feature Extraction

Only 22 images were finally used for this study. In the second phase, six gaussian filters of sizes 5×5 , 7×7 , 9×9 , 11×11 , 13×13 and 15×15 were combined, two at a time, to construct 15 DoG filters that were applied sequentially. Each one of the 15 DoG filters was applied 51 times, varying the binarization threshold in the interval [0,5] by increments of 0.1. The points obtained by applying each filter were added to the points obtained by the

previous one, deleting the repeated points. The same procedure was repeated with the points obtained by the remaining DoG filters. These points passed through the three selection methods for selecting signals (potential microcalcifications), according to region area, gray level and the gray gradient. The result was a list of 1,242,179 signals (potential microcalcifications) represented by their centroids.

The additional data included with the MIAS database define, with centroids and radii, the areas in the mammograms where microcalcifications are located. With these data and the support of expert radiologists, all the signals located in these 22 mammograms were preclassified into microcalcifications, and non-microcalcifications. From the 1,242,179 signals, only 4,612 (0.37%) were microcalcifications, and the remaining 1,237,567 (99.63%) were not. Because of this imbalanced distribution of elements in each class, an exploratory sampling was performed. Several sampling with different proportions of each class were tested and finally we decided to use a sample of 10,000 signals, including 2,500 real microcalcifications in it (25%).

After the 47 microcalcification features were extracted from each signal, the feature selection processes reduced the relevant features to only three: absolute contrast, standard deviation of the gray level and the third moment of contour sequence. Finally, a transactional database was obtained, containing 10,000 signals (2500 of them being real microcalcifications randomly distributed) and three features describing each signal.

7.3.2 Classification of Signals into Microcalcifications

In the third stage, a conventional feedforward ANN and three evolutionary ANNs were developed for the classification of signals into real microcalcifications.

The feedforward ANN had an architecture of three inputs, seven neurons in the hidden layer and one output. All the units had the sigmoid hyperbolic tangent function as the transfer function. The data (input and targets) were scaled in the range $[-1, 1]$ and divided into ten non-overlapping splits, each one with 90% of the data for training and the remaining 10% for testing. A ten-fold crossvalidation trial was performed; that is, the ANN was trained ten times, each time using a different split on the data and the means and standard deviations of the overall performance, sensitivity and specificity were reported. These results are shown in Table 7.4 on the row "BP".

For the three EANNs used to evolve signal classifiers, all of their GAs used a population of 50 individuals. We used simple GAs, with gray encoding, stochastic universal sampling selection, double-point crossover, fitness based reinsertion and a generational gap of 0.9. For all the GAs, the probability of crossover was 0.7 and the probability of mutation was $1/l$, where l is the length of the chromosome. The initial population of each GA was always initialized uniformly at random. All the ANNs involved in the EANNs are feedforward networks with one hidden layer. All neurons have biases with a constant input

Table 7.4. Mean (%) and standard deviation of the sensitivity, specificity and overall accuracy of simple backpropagation and different evolutionary methods for the classification of signals into real microcalcifications

Method	Sensitivity		Specificity		Overall	
	Mean	Std.	Mean	Std.	Std.	
					Mean	Dev.
BP	75.68	0.044	81.36	0.010	80.51	0.013
WEIGHTS	72.44	0.027	84.32	0.013	82.37	0.011
WEIGHTS+BP	75.81	0.021	86.76	0.025	84.68	0.006
PARAMETERS	73.19	0.177	84.67	0.035	83.12	0.028

of 1.0. The ANNs are fully connected, and the transfer functions of every unit is the sigmoid hyperbolic tangent function. The data (input and targets) were normalized to the interval $[-1, 1]$. For the targets, a value of “−1” means “non-microcalcification” and a value of “1” means “microcalcification”. When backpropagation was used, the training stopped after reaching a termination criteria of 20 epochs, trying also to find individual with fast convergence.

For the first approach, where a GA was used to find the ANNs weights, the population consisted of 50 individuals, each one with a length of $l = 720$ bits and representing 36 weights (including biases) with a precision of 20 bits. There were two crossover points, and the mutation rate was 0.00139. The GA ran for 50 generations. The results of this approach are shown in Table 7.4 on the row “WEIGHTS”. In the second approach, where a backpropagation training algorithm is run using the weights represented by the individuals in the GA to initialize the ANN, the population consisted of 50 individual also, each one with a length of $l = 720$ bits and representing 36 weights (including biases) with a precision of 20 bits. There were two crossover points, and the mutation rate was 0.00139 ($1/l$). In this case, each ANN was briefly trained using 20 epochs of backpropagation, with a learning rate of 0.1. The GA ran for 50 generations. The results of this approach are shown in Table 7.4 on the row “WEIGHTS+BP”.

Finally, in the third approach, where a GA was used to find the size of the hidden layer, the learning rate for the backpropagation algorithm and the range of initial weights before training, the population consisted of 50 individuals, each one with a length of $l = 18$ bits. The first four bits of the chromosome coded the learning rate in the range [0,1], the next five bits coded the lower value for the initial weights in the range $[-10,0]$, the next five bits coded the upper value for the initial weights in the range $[0,10]$ and the last four bits coded the number of neurons in the hidden layer, in the range [1,15] (if the value was 0, it was changed to 1). There was only one crossover point, and the mutation rate was 0.055555 ($1/l$). In this case, each ANN was built according to the parameters coded in the chromosome, and trained briefly with 20 epochs of backpropagation, in order to favor the ANNs that learned

quickly. The results of this approach are shown also in Table 7.4, on the row "PARAMETERS".

We performed several two-tailed Students t-tests at a level of significance of 5% in order to compare the mean of each method with the means of the other ones in terms of sensitivity, specificity and overall accuracy. We found that for specificity and overall accuracy, evolutionary methods are significantly better than the simple backpropagation method for the classification of individual microcalcifications. No difference was found in terms of sensitivity, except that simple backpropagation was significantly better than the method that evolves weights.

We can notice too that, among the studied EANNs, the one that evolves a set of initial weights and is complemented with backpropagation training is the one that gives better results. We found that in fact, again in terms of specificity and overall accuracy, the method of weight evolution complemented with backpropagation is significantly the best of the methods we studied. Nevertheless, in terms of sensitivity, this method is only significantly better than the method that evolves weights.

7.3.3 Microcalcification Clusters Detection and Classification

The process of cluster detection and the subsequent feature extraction phase generates another transactional database, this time containing the information of every microcalcification cluster detected in the images. A total of 40 clusters were detected in the 22 mammograms from the MIAS database that were used in this study. According to MIAS additional data and the advice of expert radiologists, 10 clusters are benign and 30 are malignant. The number of features extracted from them is 30, but after the two feature selection processes already discussed in previous sections, the number of relevant features we considered relevant was three: minimum diameter, minimum radius and mean radius of the clusters.

As in the stage of signal classification, a conventional feedforward ANN and three evolutionary ANNs were developed for the classification of clusters into benign and malignant. The four algorithms we use in this step are basically the same ones we used before, except that they receive as input the transactional database containing features about microcalcifications clusters instead of features about signals. Again, the means of the overall performance, sensitivity and specificity for each one of these four approaches are reported and shown in Table 7.5.

We also performed several two-tailed Students t-tests at a level of significance of 5% in order to compare the mean of each method for cluster classification with the means of the other ones in terms of sensitivity, specificity and overall accuracy. We found that the performance of evolutionary methods is significantly different and better than the performance of the simple backpropagation method, except in one case. Again, the method that evolves

Table 7.5. Mean (%) and standard deviation of the sensitivity, specificity and overall accuracy of simple backpropagation and different evolutionary methods for the classification of microcalcification clusters

Method	Sensitivity		Specificity		Overall	
	Mean	Std.	Mean	Std.	Mean	Std.
BP	55.97	0.072	86.80	0.032	76.75	0.032
WEIGHTS	72.00	0.059	92.09	0.038	86.35	0.031
WEIGHTS+BP	89.34	0.035	95.86	0.025	93.88	0.027
PARAMETERS	63.90	0.163	85.74	0.067	80.50	0.043

initial weights, complemented with backpropagation, is the one that gives the best results.

7.4 Conclusions

This chapter has presented a comparison of simple backpropagation training and three methods for combining GAs and ANNs, applied to the classification of signals into real microcalcifications and microcalcification clusters into benign and malignant, on mammograms containing microcalcifications from the MIAS database. Our experimentation suggests that evolutionary methods are significantly better than the simple backpropagation method for the classification of individual microcalcifications, in terms of specificity and overall accuracy. No difference was found in terms of sensitivity, except that simple backpropagation was significantly better than the method that only evolves weights. In the case of the classification of microcalcification clusters, we observed that the performance of evolutionary methods is significantly better than the performance of the simple backpropagation method, except in one case. Again, the method that evolves initial weights, complemented with backpropagation, is the one that gives the best results.

As future work, it would be useful to include and process other mammography databases, in order to have more examples and produce transactional feature databases more balanced and complete, and test also how different resolutions could affect system effectiveness. The size of the gaussian filters could be adapted depending on the size of the microcalcifications to be detected and the resolution of images. The correspondence between the spatial frequency of the image and the relation σ_1/σ_2 has to be thoroughly studied. Different new features could be extracted from the microcalcifications in the images and tested also.

In this study, simple GAs and ANNs were used, and more sophisticated versions of these methods could produce better results. The use of real valued chromosomes, chromosomes with indirect representation (metaheuristics, NN construction rules, etc.), use of EANNs for feature selection, etc. are other

approaches that could give different results. The inclusion of simple backpropagation training in the EANNs have consequences of longer computation times, so alternatives to backpropagation should be tested in order to reduce time costs.

Acknowledgments

This research was supported by the Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM) under the Research Chair CAT-010 and the National Council of Science and Technology of Mexico (CONACYT) under grant 41515.

References

1. American Cancer Society (ACS): Cancer facts and figures 2007. American Cancer Society, Inc., Clifton Road, NE, Atlanta, GA (2007).
2. Anttinen, I., Pamilo, M., Soiva, M., Roiha, M.: Double reading of mammography screening films: one radiologist or two? *Clin. Radiol.* **48** (1993) 414–421.
3. Balakrishnan, K., Honavar, V.: Evolutionary design of neural architectures. A preliminary taxonomy and guide to literature. Technical Report CS TR 95-01, Department of Computer Sciences, Iowa State University (1995).
4. Bankman, I. N., Tsai, J., Kim, D. W. et al.: Detection of microcalcification clusters using neural networks. In Proceedings of the 16th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Volume **16** (1994) 590–591.
5. Bazzani, A., Bollini, D., Brancaccio, R. et al.: System for automatic detection of clustered microcalcifications in digital mammograms. *International Journal of Modern Physics*, **11**(5) (2000) 901–912.
6. Betal, D., Roberts, N., Whitehouse, G. H.: Segmentation and numerical analysis of microcalcifications on mammograms using mathematical morphology. *The British Journal of Radiology*, **70** (1997) 903–917.
7. Bocchi, L., Coppini, G., Nori, J., Valli, G.: Detection of single and clustered microcalcifications in mammograms using fractal models and neural networks. *Med. Eng. Phys.*, **26**(4) (2004) 303–312.
8. Bowcock, A. M.: Breast cancer: Molecular genetics, pathogenesis, and therapeutics (Contemporary cancer research). (1st Edition). Humana Press (1999) 582 pp.
9. Cantú-Paz, E., Kamath, C.: Evolving neural networks for the classification of galaxies. In Proceedings of the Genetic and Evolutionary Computation Conference, GECCO 2002, San Francisco, CA, USA (2002) 1019–1026.
10. Caputo, B., La Torre, E., Gigante, G. E.: Microcalcification detection using a kernel bayes classifier. in Proceedings of the Third International Symposium on Medical Data Analysis, ISMDA 2002, Rome, Italy, Springer, (2002) 20–31.
11. Cheng, H. D., Lui, Y. M., Freimanis, R. I.: A novel approach to microcalcification detection using fuzzy logic technique. *IEEE Transactions on Medical Imaging*, **17**(3) (1998) 442–450.

12. Ciatto, S., Del Turo, M. R., Risso, S. et al.: Comparison of standard reading and computer aided detection (CAD) on a national proficiency test of screening mammography. *European Journal of Radiology*, **45**(2) (2003) 135–138.
13. Comer, M. L., Liu, S., Delp, E. J.: Statistical segmentation of mammograms. In 3rd International Workshop on Digital Mammography, Chicago, IL (1996) 475–478.
14. Dengler, R., Behrens, S., Desaga, J. F.: Segmentation of microcalcifications in mammograms. *IEEE Trans. Med. Imag.*, **12**(4) (1993).
15. Diyana, W. M., Larcher, J., Besar, R.: A comparison of clustered microcalcifications automated detection methods in digital mammograms. *IEEE International Conference on Acoustics, Speech and Signal Processing ICASSP 2003*, Hong Kong (2003).
16. Elmore, J. G., Miglioretti, D. L., Reisch, L. M. et al.: Screening mammograms by community radiologists: Variability in false-positive rates. *Journal of the National Cancer Institute*, **94**(18) (2002) 1373–1380.
17. El-Naqa, I., Yang, Y., Wernick, M. N. et al.: A support vector machine approach for detection of microcalcifications. *IEEE Transactions on Medical Imaging*, **21**(12) (2002) 1552–1563.
18. Fogel, D. B., Wasson III, E. C., Boughton, E. M., Porto, V. W.: Evolving artificial neural networks for screening features from mammograms. *Artificial Intelligence in Medicine*, Volume **14** (1998) 317–326.
19. Führ, H., Treiber, O., Wanninger, F.: Cluster-oriented detection of microcalcifications in simulated low-dose mammography. *Bildverarbeitung für die Medizin* (2003) 96–100.
20. Ganott, M. A., Harris, K. M., Klaman, H. M., Keeling, T. L.: Analysis of false-negative cancer cases identified with a mammography audit. *The Breast Journal*, **5**(3) (1999) 166.
21. Gavrielides, M. A.: A computer aid for the detection of suspicious microcalcification clusters in digitized mammograms. Master's thesis, Duke University (2002).
22. Goldberg, D. E.: Genetic algorithms in search, optimization and machine learning. Kluwer Academic Publishers, Boston, MA (1989).
23. Greene, F. L., Page, D. L., Fleming, I. D. et al.: AJCC Cancer Staging Manual (6th Edition). Springer (2002) 435.
24. Gulsrud, T. O.: Analysis of mammographic microcalcifications using a computationally efficient filter bank. Technical Report, Department of Electrical and Computer Engineering, Stavanger University College (2001).
25. Gupta, L., Srinath, M. D.: Contour sequence moments for the classification of closed planar shapes. *Pattern Recognition*, **20**(3) (1987) 267–272.
26. Gurcan, M. N., Chan, H.-P., Sahiner, B. et al.: Optimal neural network architecture selection: Improvement in computerized detection of microcalcifications, *Academic Radiology* **9**(4) (2002) 420–429.
27. Halkiotis, S., Mantas, J., Botsis, T.: Computer-aided detection of clustered microcalcifications in digital mammograms. In 5th European Conference in Systemic Science, Crete (2002).
28. Haykin, S.: Neural networks: A comprehensive foundation. Prentice Hall (1999).
29. Hernández-Cisneros, R. R., Terashima-Marín, H., Conant-Pablos, S. E.: Comparison of class separability, forward sequential search and genetic algorithms

- for feature selection in the classification of individual and clustered microcalcifications in digital mammograms. International Conference in Image Analysis and Recognition ICIAR 2007, Springer Verlag, Montreal, Canada (2007) 911–922.
- 30. Hernández-Cisneros, R. R., Terashima-Marín, H.: Classification of individual and clustered microcalcifications in digital mammograms using evolutionary neural networks, MICAI 2006, Springer Verlag, Apizaco, Tlaxcala, Mexico (2006) 1200–1210.
 - 31. Hernández-Cisneros, R. R., Terashima-Marín, H.: Evolutionary neural networks applied to the classification of microcalcification clusters in digital mammograms. In Proceedings of the 2006 IEEE Congress on Evolutionary Computation, Vancouver, BC, Canada (2006) 2459–2466.
 - 32. Hernández-Cisneros, R. R., Terashima-Marín, H.: Feature selection for the classification of microcalcification clusters in digital mammograms using genetic algorithms. GECCO Workshop on Medical Applications of Genetic and Evolutionary Computation MedGEC 2006, Seattle, USA (2006).
 - 33. Holland, J. H.: Adaptation in natural and artificial systems. University of Michigan Press, Ann Arbor (1975).
 - 34. Hojjatoleslami, A., Sardo, L., Kittler, J.: An RBF based classifier for the detection of microcalcifications in mammograms with outlier rejection capability. International Conference on Neural Networks, Volume 3 (1997) 1379–1384.
 - 35. Hong, B.-W., Brady, M.: Segmentation of mammograms in topographic approach. In IEE International Conference on Visual Information Engineering, Guildford, UK (2003).
 - 36. Hu, M.-K.: Visual pattern recognition by moment invariants. IRE Trans. Information Theory, Vol. IT-8 (1962) 179–187.
 - 37. Ibrahim, N., Fujita, H., Hara, T., Endo, T.: Automated detection of clustered microcalcifications on mammograms: CAD system application to MIAS database. Physics in Medicine and Biology, 42(12) (1997) 2577–2589.
 - 38. Kim, J. K., Park, H. W.: Statistical textural features for detection of microcalcifications in digital mammograms. IEEE Transactions on Medical Imaging, 18(3) (1999) 231–238.
 - 39. Kim, J. K., Park, J. M., Song, S. S., Park, H. W.: Detection of clustered clustered microcalcifications on mammograms using surrounding region dependence method and artificial neural network. J. VLSI Signal Process., Volume 18 (1998) 251–262.
 - 40. Kozlov, A., Koller, D.: Nonuniform dynamic discretization in hybrid networks. In Proceedings of the 13th Annual Conference of Uncertainty in AI (UAI), Providence, Rhode Island, USA (2003) 314–325.
 - 41. Lasztovicza, K., Pataki, B., Székely, N., Tóth, N.: Neural network based microcalcification detection in a mammographic CAD system. In Intelligent Data Acquisition and Advanced Computing Systems: Technology and Applications, IDAACS 2003, Lviv, Ukraine (2003).
 - 42. Lefebvre, F., Benali, H., Gilles, R. et al. A fractal approach to the segmentation of microcalcifications in digital mammograms. Med. Phys., 22(4) (1995) 381–390.
 - 43. Lemaur, G., Drouiche, K., DeConinck, J.: Highly regular wavelets for the detection of clustered microcalcifications in mammograms. IEEE Transactions on Medical Imaging, 25(3) (2003) 393–401.

44. Li, S., Hara, T., Hatanaka, Y. et al.: Performance evaluation of a CAD system for detecting masses on mammograms by using the MIAS database. *Medical Imaging and Information Science*, **18**(3) (2001) 144–153.
45. Li, H., Liu, K. J., Lo, S. C.: Fractal modeling and segmentation for the enhancement of microcalcifications in digital mammograms. *IEEE Trans. Med. Imaging*, **16**(6) (1997) 785–798.
46. Linguraru, M. G., Brady, J. M., Yam, M.: Detection of microcalcifications using SMF. In 6th International Workshop of Digital Mammography (Lecture Notes in Computer Science), Springer Verlag (2002).
47. Liu, J., Hwang, W., Chen, M.: Estimation of 2-D noisy fractional brownian movement and its applications using wavelets. *IEEE Transactions on Image Processing*, **9**(8) (2000) 1407.
48. McGarry, G.: Performance of the generalized gaussian distribution for detection of calcifications in mammographic images. Signal Processing Research Centre, Queensland University of Technology, Brisbane, Australia (1999).
49. Melloul, M., Joskowicz, L.: Segmentation of microcalcifications in X-ray mammograms using entropy thresholding. In Computer Assisted Radiology and Surgery, CARS 2002, Springer (2002).
50. Nishikawa, R. M.: Computer aided detection of clustered microcalcifications: An improved method for grouping detected signals. *Medical Physics*, **20**(6) (1993) 1661–1666.
51. Norhayati, I., Hiroshi, F., Takeshi, H., Tokiko, E.: Automated detection of clustered microcalcifications on mammograms: CAD system application to MIAS database. *Phys. Med. Biol.*, **42** (1997) 2577–2589.
52. Ochoa, E. M.: Clustered microcalcification detection using optimized difference of gaussians. Master's Thesis, Air Force Institute of Tech. Wright-Patterson (1996).
53. Oporto-Díaz, S., Hernández-Cisneros, R. R., Terashima-Marín H.: Detection of microcalcification clusters in mammograms using a difference of optimized gaussian filters. In Proceedings of the International Conference in Image Analysis and Recognition ICIAR 2005, Toronto, Canada (2005) 998–1005.
54. Papadopoulissa, A., Fotiadisb, D. I., Likasb, A.: An automatic microcalcification detection system based on a hybrid neural network classifier. *Artificial intelligence in Medicine*, **25** (2002) 149–167.
55. Papik, K., Molnar, B., Schaefer, R. et al.: Application of neural networks in medicine - a review. *Med. Sci. Monit.*, **4**(3) (1998) 538–546.
56. Patrocinio, A. C., Schiabel, H., Benatti, R. H. et al.: Investigation of clustered microcalcification features for an automated classifier as part of a mammography CAD scheme. Engineering in Medicine and Biology Society. Proceedings of the 22nd Annual International Conference of the IEEE Volume **2** (2000) 1203–1205.
57. Penny, W., Frost, D.: Neural networks in clinical medicine. *Med. Decis. Making*, **16** (1996) 386–398.
58. Polakowski, W. E., Cournoyer, D. A., Rogers, S. K. et al.: Computer-aided breast cancer detection and diagnosis of masses using difference of gaussians and derivative-based feature saliency. *IEEE Transactions on Medical Imaging*, **16**(6) (1997) 811–819.
59. Ricketts, I. W., Cairns, A. Y., Folkes, D. et al.: The automated detection of clusters of microcalcifications. In IEE Colloquium: Applications of Image Processing in Mass Health Screening, Digest No. 1992/056, London (1992) 13–15.

60. Sajda, P., Spence, C., Pearson, J.: Learning contextual relationships in mammograms using a hierarchical pyramid neural network. *IEEE Transactions on Medical Imaging*, **21**(3) (2002) 239–250.
61. Salfity, M. F., Kaufmann, G. H., Granitto, P., Ceccatto, H. A.: Automated detection and classification of clustered microcalcifications using morphological filtering and statistical techniques. In 5th International Workshop on Digital Mammography, Toronto, Canada (2000).
62. Sehad, S., Desarnaud, S., Strauss, A.: Artificial neural classification of clustered microcalcifications on digitized mammograms. In Proceedings of the IEEE International Conference on Systems, Man and Cybernetics, Volume 5 (1997) 4217–4222.
63. Skinner, A., Broughton, J. Q.: Neural networks in computational material science: training algorithms. *Modeling and Simulation in Material Science and Engineering*, **3** (1995) 371–390.
64. Sordo, M.: Introduction to neural networks in healthcare [WWW document]. Open Clinical (2002) URL: <http://www.openclinical.org/docs/int/neuralnetworks011.pdf>
65. Strausz, G., Horváth, G., Pataki, B. et al.: Intelligent solution for mammography image diagnosis. In Engineering Application of Neural Networks Conference EANN 2003, Malaga, Spain (2003).
66. Suckling, J., Parker, J., Dance, D. et al.: The Mammographic Images Analysis Society digital mammogram database. Excerpta Medica International Congress Series, **1069** (1994) 375–378. URL: <http://www.wiau.man.ac.uk/services/MIAS/MIASweb.html>
67. Thurfjell, E. L., Lernevall, K. A., Taube, A. A. S.: Benefit of independent double reading in a population-based mammography screening program. *Radiology*, **191** (1994) 241–244.
68. Treiber, O., Wanninger, F., Führ, H. et al.: An adaptive algorithm for the detection of microcalcifications in simulated low-dose mammography. GSF - National Research Center for Environment and Health (2002) 1–24.
69. Ustymowics, M., Nieniewski, M.: Clustering microcalcifications in mammograms by means of morphology based strategy. In Fourth IEEE Benelux Signal Processing Symposium, Hilvarenbeek, Netherlands (2004).
70. Verma, B.: A neural network based technique to locate and classify microcalcifications in digital mammograms. In Proceedings of the IEEE International Conference on Neural Networks, Volume 3 (1998) 1790–1793.
71. World Health Organization: Fact sheet No. 297: Cancer [WWW document]. (2006) URL: <http://www.who.int/mediacentre/factsheets/fs297/en/index.html>
72. Woods, K., Doss, C., Bowyer, K. et al.: A neural network approach to microcalcification detection. IEEE 1992 Nuclear Science Symposium and Medical Imaging Conference, Orlando, FL (1992) 1273–1275.
73. Wróblewska, A., Boninski, P., Przelaskowski, A., Kazubek, M.: Segmentation and feature extraction for reliable classification of microcalcifications in digital mammograms, *Opto Electronics Review*, **11**(3) (2003) 227–235.
74. Yao, X.: Evolution of connectionist networks. In Preprints Int. Symp. AI, Reasoning and Creativity, Queensland, Australia, Griffith Univ. (1991) 49–52.
75. Yao, X.: Evolving artificial neural networks. In Proceedings of the IEEE, **87**(9) (1999) 1423–1447.

76. Yu, S., Guan, L.: A CAD system for the automated detection of clustered microcalcifications in digitized mammogram films. *IEEE Transactions on Medical Imaging*, **19**(2) (1999) 115–126.
77. Zhao, D., Shridhar, M., Daut, D. G.: Morphology on detection of calcifications in mammograms. In *IEEE International Conference on Acoustics, Speech and Signal Processing ICASSP 92*, Volume **3** (1992) 129–132.
78. Zheng, B., Qian, W., Clarke, L. P.: Digital mammography: mixed feature neural network with spectral entropy decision for detection of microcalcifications. *IEEE Trans. Med. Imag.*, **15**(5) (1996) 589–597.