Computer Aided Diagnosis in Primary Brain Cancers of Dogs and Cats

Current Problem or Opportunity

The most common types of primary intracranial cancer in dogs are meningioma, glioma, and choroid plexus tumors, generally occurring in middle-aged to older dogs.

Meningiomas and gliomas account for most of the total primary brain neoplasms in dogs and differentiating between these two forms is extremely important in choosing the correct therapy.

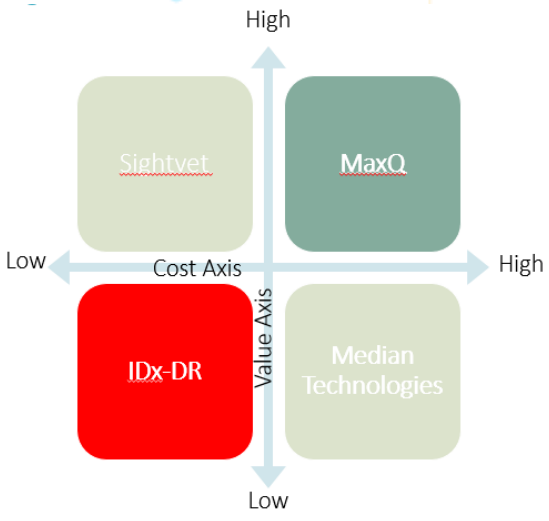
Although a prognosis toward the existence of a particular tumor type may or may not be supported by some imaging features, the differentiation between meningeal-based (within the membranes surrounding the brain) and intra-axial (within the brain) lesions may occasionally be challenging.

A Computer-Aided Diagnosis (CAD) tool can quickly and accurately differentiates between primary brain tumors.

Competitive analysis

MaxQ AI designs and manufactures new tools to support a clinical assessment of intracranial hemorrhage (ICH).

Another CAD company uses a device called IDx-DR which is a software program that uses an artificial intelligence algorithm to analyze images of the eye taken with a retinal camera and to provide a screening



decision.

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Abstract:

In the dog, primary intracranial neoplasia represents ~2–5% of all cancers and is especially common in certain breeds including English and French bulldogs and Boxers. Neoplasm is a new and abnormal growth of tissue in some part of the body, especially as a characteristic of cancer. The most common types of primary intracranial cancer in the dog are meningioma, glioma, and choroid plexus tumors, generally occurring in middle aged to older dogs. Much work has recently been done to understand the characteristic imaging and clinic pathologic features of these tumors. Distinguishing between meningeal-based and intra-axial lesions by means of magnetic resonance (MR) imaging findings may occasionally be challenging. Meningiomas and gliomas account for most of the total primary brain neoplasms in dogs, and differentiating between these two forms is mandatory in choosing the correct therapy. Brain tumors are commonly treated with surgery, radiation therapy, and/or chemotherapeutic regimens but early detection is an important in the treatment procedure.

The gross and histologic landscape of these tumors in the dog compare favorably to their human counterparts with many similarities noted in histologic patterns, subtype, and grades. Data informing the underlying molecular abnormalities in the canine tumors have only begun to be unraveled, but reveal similar pathways are mutated between canine and human primary intracranial neoplasia.

What is an MR IMAGE?

Magnetic Resonance Imaging (MRI or MR) is the most advanced diagnostic imaging tool available. This safe, non-invasive procedure allows more complete viewing of the body than any other modality. This technology uses no ionizing radiation, such as x-rays. The patient is placed onto a table surrounded by a powerful magnet. Minute signals are produced as the body responds to the magnetic field. These signals are converted to a cross-sectional image, allowing radiologists and other specialists to look deep into the body for injury or disease.

The MRI Service performs hundreds of examinations per year on dogs, cats, and exotic pets. Now seen as the gold standard for examining the brain and spine, MRI has replaced many of the more invasive procedures of the past. Common diseases diagnosed include spinal disk herniation, brain tumors, trauma of the brain and spine, strokes, and brain malformations. MRI has led to earlier and more accurate diagnosis for these and other diseases. Important advances in the knowledge of spinal cord injury from disk herniation.

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MRI is also a powerful tool for examining the skeleton, including bone, tendons, ligaments, and joints. As the technology advances, specialists are finding endless uses for MRI. The uses of MRI include studies of the heart in motion, tracking of nerve fibers in the brain and spine, and spectroscopy which allows more definitive typing of brain tumors without the need for biopsy.

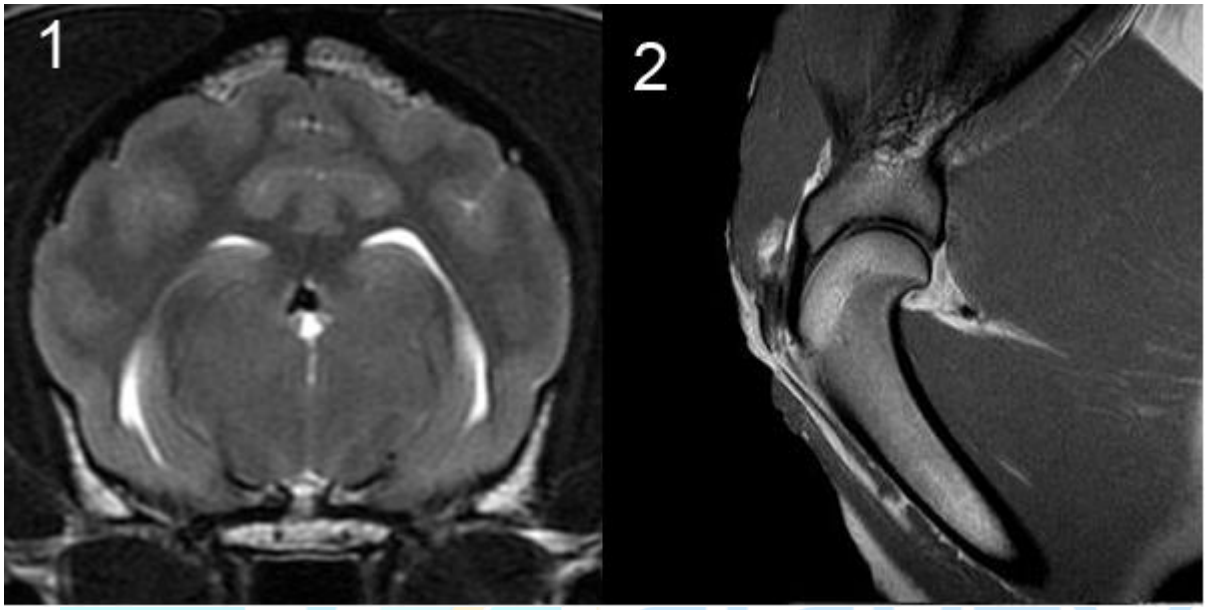

Figure 1. **(Left)** An MRI image of a normal dog brain **(right)** An MRI image of a normal dog shoulder

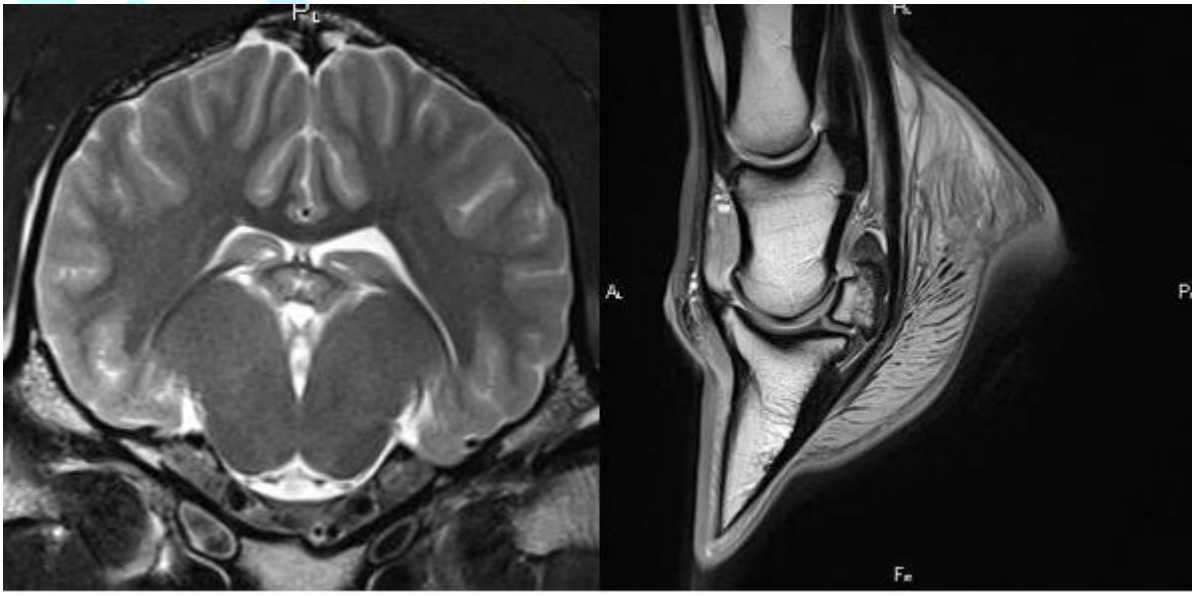

Figure 2 (left) An MRI image of a normal horse brain (right) An MRI image of a normal horse foot

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What is T1 and T2 images?

Repetition Time (TR) is the amount of time between successive pulses sequences applied to the same slice. Time to Echo (TE) is the time between the delivery of the RF pulse and the receipt of the echo signal.

Tissue can be characterized by two different relaxation times – T1 and T2. T1 (longitudinal relaxation time) is the time constant which determines the rate at which excited protons return to equilibrium. It is a measure of the time taken for spinning protons to realign with the external magnetic field. T2 (transverse relaxation time) is the time constant which determines the rate at which excited protons reach equilibrium or go out of phase with each other. It is a measure of the time taken for spinning protons to lose phase coherence among the nuclei spinning perpendicular to the main field.

The most common MRI sequences are T1-weighted and T2-weighted scans. T1-weighted images are produced by using short TE and TR times. The contrast and brightness of the image are predominately determined by T1 properties of tissue. Conversely, T2-weighted images are produced by using longer TE and TR times. In these images, the contrast and brightness are predominately determined by the T2 properties of tissue.

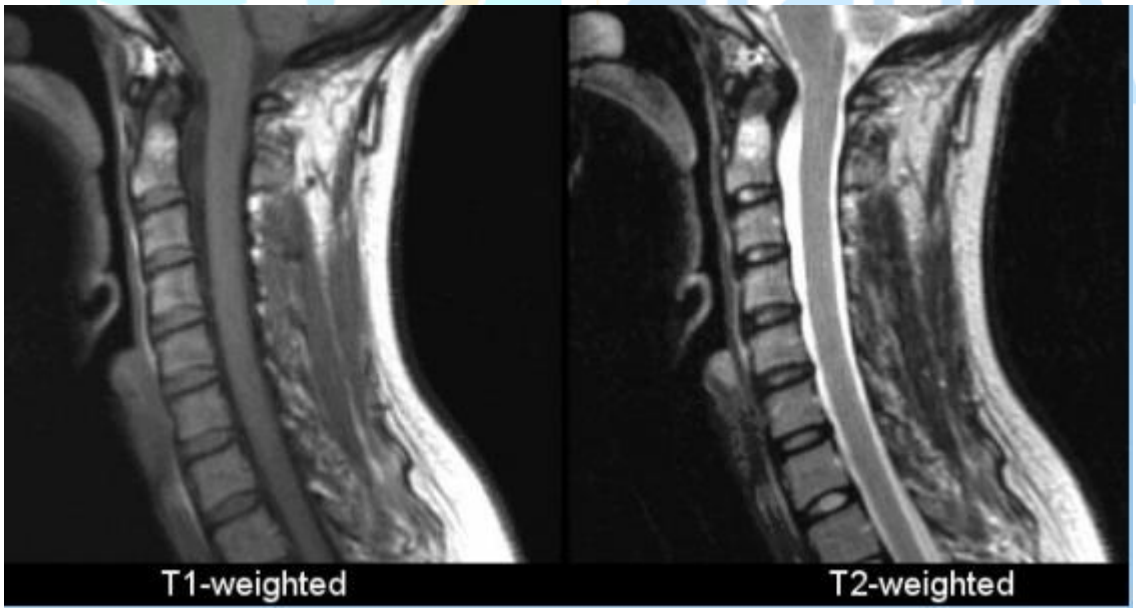

Figure 3:T1 and T2 MR Images

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How is prevalence of brain tumor in dogs?

Dogs are the only mammalian species besides humans in which spontaneous brain tumors arise frequently (1–4). The estimated incidence of canine nervous system tumors is reported as 14.5 cases per 100,000 (5). Other studies indicate that intracranial neoplasms are observed in 2–4.5% of dogs that are subjected to post-mortem examinations (2, 4, 5).

In dogs, ~90% of primary brain tumors (PBT) encountered in clinical practice are represented by meningiomas (~50%), gliomas (~35%), and choroid plexus tumors (CPT; ~7%), although the distribution of specific PBT in individual studies varies considerably (1–5). Other PBT, including ependymoma, germinoma, and embryonal tumors are all extremely rare, poorly defined outside of scattered case reports and series, and will not be considered in this review. Secondary brain tumors (SBT) comprise approximately one-half of all canine intracranial tumors, with hemangiosarcoma (29–35%), lymphoma (12–20%), and metastatic carcinomas (11–20%) accounting for 77–86% of all SBT (4, 6).

Brain tumors in dogs occur at any age and in any breed, and there are no reported sex predispositions. However, most PBT and SBT occur in middle-aged to older dogs, with the majority of cases described being > 5 years of age (3, 4, 7, 8). Median ages at diagnosis for dogs with gliomas, meningiomas, and CPT are 8 years, 10.5 years, and 5.5 years, respectively (3, 4, 7, 8). There is a propensity for intracranial tumors identified in juvenile animals to be neuroepithelial tumors of glial, neuronal, or embryonal origin (4, 9). One study identified a statistically significant linear relationship between age and body weight and the occurrence of PBT, and large breed dogs were at significantly increased risk for developing meningiomas and CPT (4). Golden retrievers, boxers, miniature schnauzers, and rat terriers have been identified as breeds in which intracranial meningiomas are overrepresented (3, 4).

Although CPT were also overrepresented in Golden Retrievers in one study (8), this breed predisposition was not substantiated in a subsequent investigation (4). Gliomas (astrocytomas, oligodendrogliomas, and undefined gliomas) are highly overrepresented in several brachycephalic breeds including boxers, Boston terrier, bullmastiffs, and English and French bulldogs (2–4). A locus on canine chromosome (CFA) 26 has been strongly associated with glioma risk across multiple dog breeds, with regional mapping revealing single nucleotide variants in three neighboring genes *DENR, CAMKK2*, and *P2RX7* that are highly associated with glioma susceptibility (10). The *CAMKK2* and *P2RX7* genes are relevant to the development or progression of human cancers (10). Further characterization of these genetic associations may provide insight into the

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drivers of gliomas in dogs and humans, identify new therapeutic targets, or decrease the incidence of gliomas in dogs through selective breeding strategies.

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Pathophysiology and Clinical Signs

PBT are intracranial mass lesions that cause clinical signs of brain dysfunction by directly invading or compressing brain tissue and secondarily by causing peritumoral edema, neuroinflammation, obstructive hydrocephalus, and intracranial hemorrhage (11). Compensatory autoregulatory mechanisms, such as decreased cerebrospinal fluid (CSF) production and shifting of CSF into the spinal subarachnoid space, are effective at maintaining the intracranial pressure within physiologic ranges in the early phases of tumor growth. For slow-growing tumor types, such as meningiomas, intracranial pressure-volume homeostatic regulatory mechanisms can often remain intact despite large tumor olumes associated with significant mass effect. However, with progressive increases in tumor volume, autoregulatory mechanisms are eventually overwhelmed and intracranial hypertension (ICH) develops. ICH and the resulting cerebral hypoperfusion is the common pathophysiologic denominator underlying many of the mechanisms of tumor-associated brain injury. Acute clinical deterioration observed in animals with brain tumors and ICH is often the result of vasogenic edema, obstructive hydrocephalus, brain ischemia or hemorrhage, brain herniation, or combinations of these mechanisms (11).

A brain tumor should be considered a differential diagnosis in any middle-aged or older dog with a clinical history consistent with brain dysfunction, especially when clinical signs are progressive. Seizures are the most common clinical manifestation of intracranial neoplasia, and are observed in ~50% of dogs with prosencephalic tumors (3, 12–17). Structural causes of epilepsy, such as brain tumors, should also be suspected in dogs that experience a new onset of seizure activity after 5 years of age, particularly in predisposed breeds (14). Risk factors for tumor-associated structural epilepsy identified on MRI scans in dogs include the presence of tumor involving the frontal lobe, falcine or subtentorial brain herniations, and

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marked contrast enhancement of the tumor (16). The pathophysiology of tumor-related epilepsy is currently poorly understood, but both the tumoral and peritumoral microenvironments may contribute to epileptogenic phenotypes owing to disordered neuronal connectivity and regulation, impaired glial cell function, and the presence of altered vascular supply and permeability (18–20). Central vestibular dysfunction is the most common clinical sign associated with brain tumors originating in the caudal brainstem (14, 21). Dogs with brain tumors may also present with non-specific clinical signs, such as lethargy, inappetence, and weight loss (22). Tumors in the fronto-olfactory region are often associated with only historical evidence of brain disease such as seizures or behavioral changes and a normal interictal neurological examination.

Most PBT in dogs occur as solitary mass lesions, and tumors involving forebrain structures are more common than those in the brainstem (3, 4, 21). In many cases with solitary masses, the neurological deficits observed reflect the focal neuroanatomic area of the brain containing the tumor. However, dogs with PBT or SBT may also present with neurological deficits indicative of multifocal intracranial disease.

Multifocal clinical signs may result from several phenomena. The tumor or its secondary effects (vasogenic edema, brain herniation, or hemorrhage) may involve more than one region of the brain, which has been reported in up to 50% of dogs with solitary PBT (3). The phenotypes of some PBT, such as butterfly glioblastomas, diffuse glioma, or leptomeningeal oligodendrogliomatosis, are characterized by invasion of both cerebral hemispheres or diffuse brain or meningeal involvement (23–26). Multiple discrete tumor foci may also be present, which occurs occasionally in canine meningiomas and histiocytic sarcomas (1, 27). Rare reports describing synchronous PBT of different histologies, and concurrent PBT and SBT also exist (28, 29). PBT, and particularly choroid plexus carcinomas, may metastasize within the CNS by a unique mechanism termed drop metastases (8, 11, 30). This involves exfoliation of cancer cells into and circulation within the CSF, with implantation of tumor foci distant from the site of the primary tumor in the ventricular system or subarachnoid space.

Brain neoplasms are a primary concern in adult dogs, with an overall reported prevalence of 4.5% [1]. Treatment options for brain tumors in dogs include symptomatic management, chemotherapy, surgery, radiation therapy, surgery combined with chemotherapy and/or radiation therapy [2]. When symptomatic management or radiation therapy is chosen as the treatment option, histopathological analysis of the lesions is usually not performed and the diagnosis is based only on interpretation by the imaging expert [3]. Although some imaging features may be used to increase or decrease suspicion of a particular tumor type, the distinction between meningeal-based and intra-axial lesions may occasionally be challenging [4]. Meningiomas and gliomas account for most of the total primary brain neoplasms in dogs [1], and differentiating between

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these two forms is mandatory in choosing the correct therapy The role of diagnostic imaging grows progressively more important as the demand for high quality veterinary care constantly increases. In such a scenario, a thorough standardization in interpretation of diagnostic images becomes ever more desirable. The possible applications of a texture analysis-based approach on other diagnostic imaging techniques such as MRI [5] or computed tomography [6] have only seldom been investigated in veterinary medicine. On the other hand, several studies exploring the use of texture analysis to establish the relationship between ultrasonography and pathology have been published [7–13]. The main purpose of these studies was to overcome the inherent limitations of ultrasonography in identifying subtle changes in the appearance of parenchymal organs (mainly kidney and liver) caused by degenerative pathologies.
In the present work we have tried to take advantage of CNNs in the extraction and analysis of complex data patterns in order to distinguish between meningiomas and gliomas in pre- and post-contrast T1 images and T2 images. Furthermore, we have developed an image classifier, which could be prospectively used in a clinical scenario, to predict whether a lesion is a meningioma or a glioma; such a classifier is based on the combination of CNN and MRI sequence displaying the highest accuracy.

Classification in machine learning

In machine learning and statistics, classification is a supervised learning approach in which the computer program learns from the data input given to it and then uses this learning to classify new observation. This data set may simply be bi-class (like identifying whether the person is male or female or that the mail is spam or non-spam) or it may be multi-class too. Some examples of classification problems are: speech recognition, handwriting recognition, bio metric identification, document classification etc.

Here we have the types of classification algorithms in Machine Learning:

1. Linear Classifiers: Logistic Regression, Naive Bayes Classifier

2. Nearest Neighbor

3. Support Vector Machines

4. Decision Trees

5. Boosted Trees

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6. Random Forest

7. Neural Networks

8. Deep learning

DEEP learning

Artiftial Neural Networks & Deep learning

Artificial neurons

Before understanding ANN, first, let's understand what neurons are and how neurons in our brain actually work. A neuron can be defined as the basic computational unit of the human brain. Our brain contains approximately 100 billion neurons. Each and every neuron is connected through synapses. Neurons receive input from the external environment, sensory organs, or from the other neurons through a branchlike structure called dendrites, as can be seen in the following diagram. These inputs are strengthened or weakened, that is, they are weighted according to their importance and then they are summed together in the soma (cell body). Then, from the cell body, these summed inputs are processed and move through the axons and are sent to the other neurons. The basic single biological neuron is shown in the following diagram:

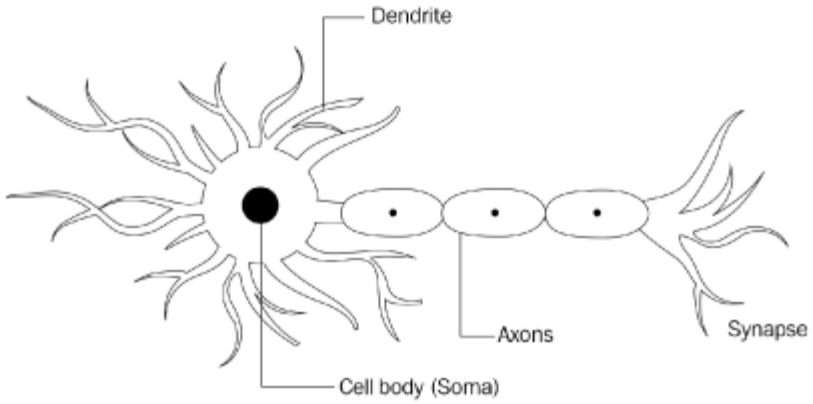

Figure 4: a single neuron

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Now, how do artificial neurons work? Let's suppose we have three inputs, x1, x2, and x3, to predict output y. These inputs are multiplied by weights, w1, w2, and w3, and are summed together, that is, x1.w1 + x2.w2 + x3.w3. But why are we multiplying these inputs with weights? Because all of the inputs are not equally important in calculating the output y. Let's say that x2 is more important in calculating the output compared to the other two inputs. Then, we assign a high value to w2 rather than for the other two weights. So, upon multiplying weights with inputs, x2 will have a higher value than the other two inputs. After multiplying inputs with the weights, we sum them up and we add a value called bias *b*. So,

$z = (x1.w1 + x2.w2 + x3.w3) + b$, that is:

$$Z = \sum (inputs * weights) + bias$$

It seems regression equation ($z = mx + b$) Where m is the weights (coefficients), x is the input, and b is the bias (intercept). Well, yes. Then what is the difference between neurons and linear regression? In neurons, we introduce non-linearity to the result, z, by applying a function f() called the activation or transfer function. So, our output is y = f(z). A single artificial neuron is shown in the following diagram:

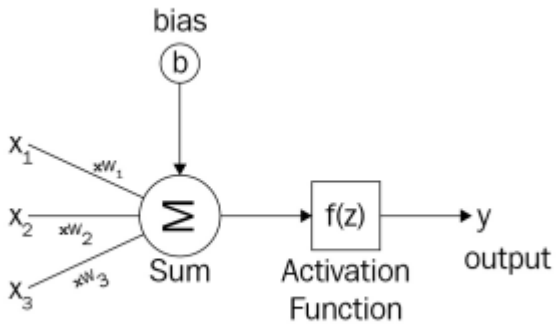

Figure 5: ANN simple diagram it is similar to linear regression

In neurons, we take the input x, multiply the input by weights w, and add bias b before applying the activation function f(z) to this result and predict the output y

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ANNs

Neurons are cool, but single neurons cannot perform complex tasks, which is why our brain has billions of neurons, organized in layers, forming a network. Similarly, artificial neurons are arranged in layers. Each and every layer will be connected in such a way that information is passed from one layer to another. A typical ANN consists of the following layers:

- Input layer
- Hidden layer
- Output layer

Each layer has a collection of neurons, and the neurons in one layer interact with all the neurons in the other layers. However, neurons in the same layer will not interact with each other. A typical ANN is shown in the following diagram:

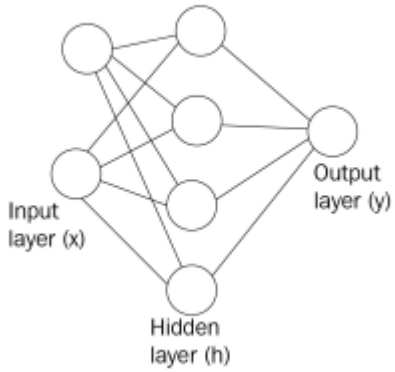

Figure 6: a typical ANN structure

Input layer

The input layer is where we feed input to the network. The number of neurons in the input layer is the number of inputs we feed to the network. Each input will have some influence on predicting the output and this will be multiplied by weights, while bias will be added and passed to the next layer.

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Hidden layer

Any layer between the input layer and the output layer is called a hidden layer. It processes the input received from the input layer. The hidden layer is responsible for deriving complex relationships between input and output. That is, the hidden layer identifies the pattern in the dataset. There can be any number of hidden layers, however we have to choose a number of hidden layers according to our problem. For a very simple problem, we can just use one hidden layer, but while performing complex tasks like image recognition, we use many hidden layers where each layer is responsible for extracting important features of the image so that we can easily recognize the image. When we use many hidden layers, the network is called a deep neural network.

Output layer

After processing the input, the hidden layer sends its result to the output layer. As the name suggests, the output layer emits the output. The number of neurons in the output layer relates to the type of problem we want our network to solve. If it is a binary classification, then the number of neurons in the output layer tells us which class the input belongs to. If it is a multi-class classification say, with five classes, and if we want to get the probability of each class being an output, then the number of neurons in the output layer is five, each emitting the probability. If it is a regression problem, then we have one neuron in the output layer.

Activation functions

Activation functions are used to introduce nonlinearity in neural networks. We apply the activation function to the input which is multiplied by weights and added to the bias, that is, f(z), where z = (input * weights) + bias

Deep learning

Deep learning is a collection of algorithms and type of machine learning (ML) and artificial intelligence (AI) technique that teaches computers to learn by example. Convolutional Neural Networks (CNN) is branch of deep learning have been recently employed to solve problems for medical image analysis fields. For overcoming limited size dataset problem it is possible to use pre-trained CNN called GoogleNet, a process called "transfer learning". This process helps to train our networks by small amount of images.

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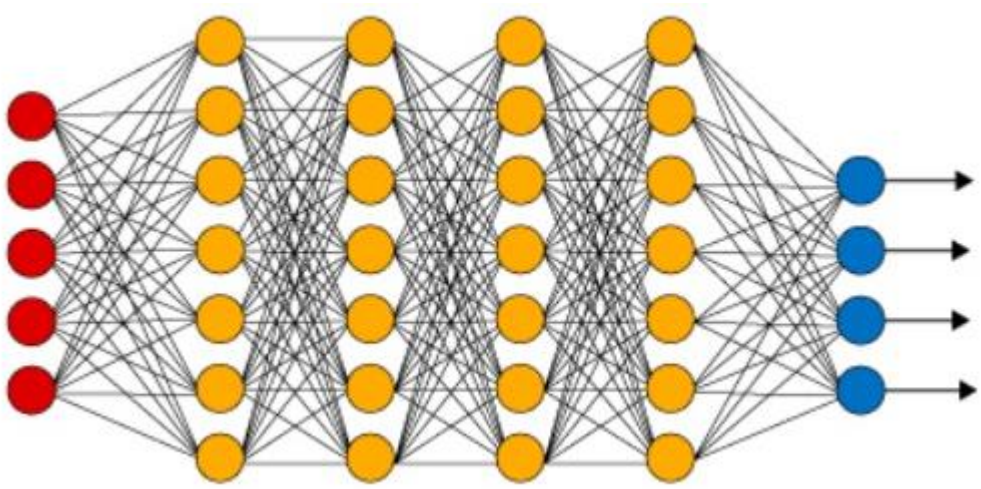

Figure 7: Deep neural network

Convolutional Neural Network

A Convolutional Neural Network (ConvNet/CNN) is a Deep Learning algorithm which can take in an input image, assign importance (learnable weights and biases) to various aspects/objects in the image and be able to differentiate one from the other. The pre-processing required in a ConvNet is much lower as compared to other classification algorithms. While in primitive methods filters are hand-engineered, with enough training, ConvNets have the ability to learn these filters/characteristics.

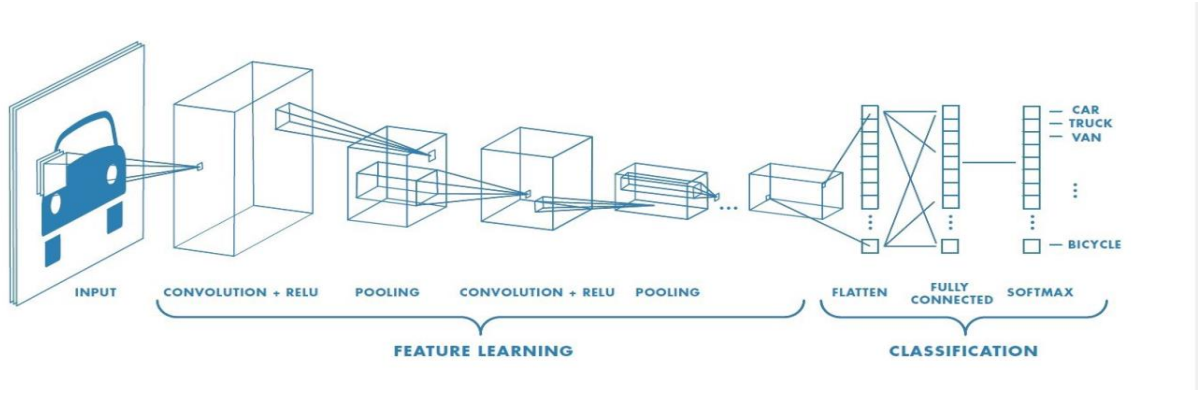

Figure 8: whole parts of deep leering

The architecture of a ConvNet is analogous to that of the connectivity pattern of Neurons in the Human Brain and was inspired by the organization of the Visual Cortex. Individual neurons respond to stimuli only in

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a restricted region of the visual field known as the Receptive Field. A collection of such fields overlap to cover the entire visual area.

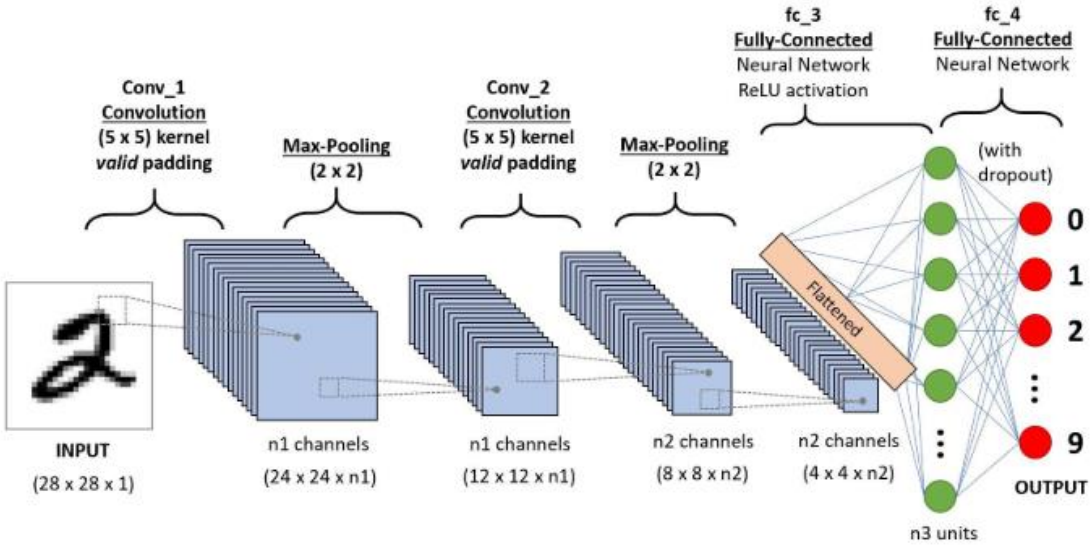

Figure 9:CNN architecture

Transfer Learning:

Transfer learning make use of the knowledge gained while solving one problem and applying it to a different but related problem. For example, knowledge gained while learning to recognize cars can be used to some extent to recognize trucks.

Pre-Training

When we train the network on a large dataset (for example: ImageNet), we train all the parameters of the neural network and therefore the model is learned. It may take hours on your GPU.

Fine Tuning

We can give the new dataset to fine tune the pre-trained CNN. Consider that the new dataset is almost similar to the original dataset used for pre-training. Since the new dataset is similar, the same weights can be used for extracting the features from the new dataset.

1. If the new dataset is very small, it's better to train only the final layers of the network to avoid overfitting, keeping all other layers fixed. So remove the final layers of the pre-trained network. Add new layers. Retrain only the new layers.

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2. If the new dataset is very much large, retrain the whole network with initial weights from the pretrained model.

How to fine tune if the new dataset is very different from the original dataset?

The earlier features of a ConvNet contain more generic features (e.g. edge detectors or color blob detectors), but later layers of the ConvNet becomes progressively more specific to the details of the classes contained in the original dataset.

The earlier layers can help to extract the features of the new data. So it will be good if you fix the earlier layers and retrain the rest of the layers, if you got only small amount of data. If you have large amount of data, you can retrain the whole network with weights initialized from the pre-trained network.

Proposed method

Computer-aided diagnosis (CAD) of lesion classification is a current active area in medical. The Improvement of the computer hardwares and optimized Algorithm of image processing and accessibility to data for data science, significantly assists to vets and radiologists in decision-making in various medical problems.

Machine learning, a branch of artificial intelligence, has been utilized to assess risk and inform practice management, and predict individual outcomes, length of stay, recommend treatments, and personalized medicine Supervised machine learning algorithms such as support vector machine (SVM), K-nearest neighborhood are known as traditional method but our suggested method convolution neural network, consistently have superior accuracy compared with other machine learning algorithms. To this end we are suggested CAD system for classifying between meningiomas and gliomas.

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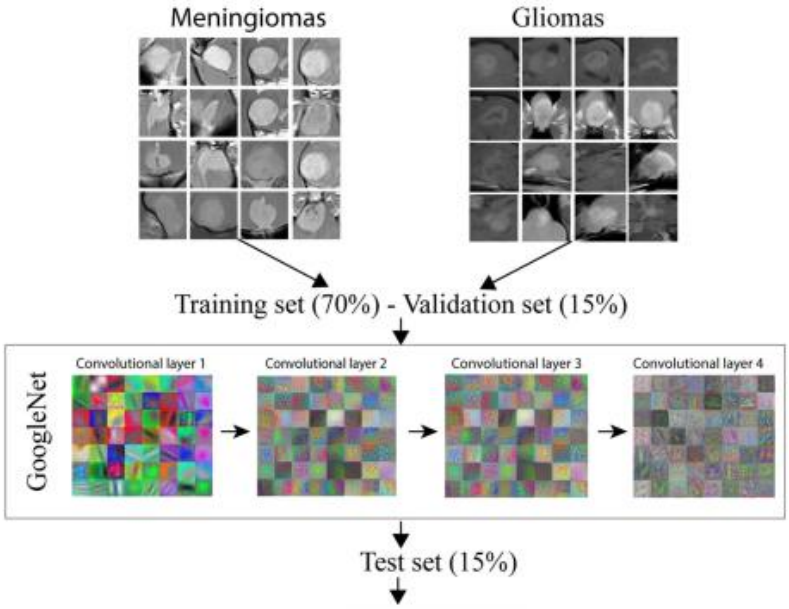

Figure 10: Simplified representation of the analytical method

Deeper convolutional layers are able to detect more complex features (Fig 10). Pooling layers are used to reduce data volume, decreasing the size of the feature maps while retaining the most important information. The dense layers are the classification layers and are the equivalent of a classical artificial neural network; a set of interconnected neurons that analyses an input and generate an output to make predictions on new data. The features (along with their weights and biases) derived from the ImageNet database were then adjusted on the new dataset to predict the labels of the new images (transfer learning)

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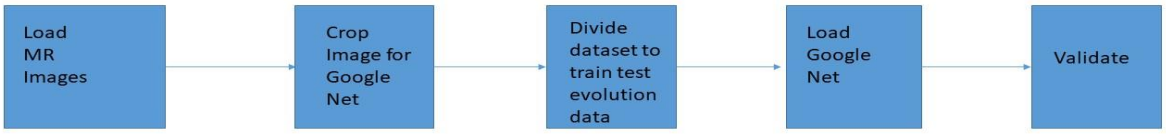

Figure 11: Proposed algorithm method

EXECUTIVE SUMMARY

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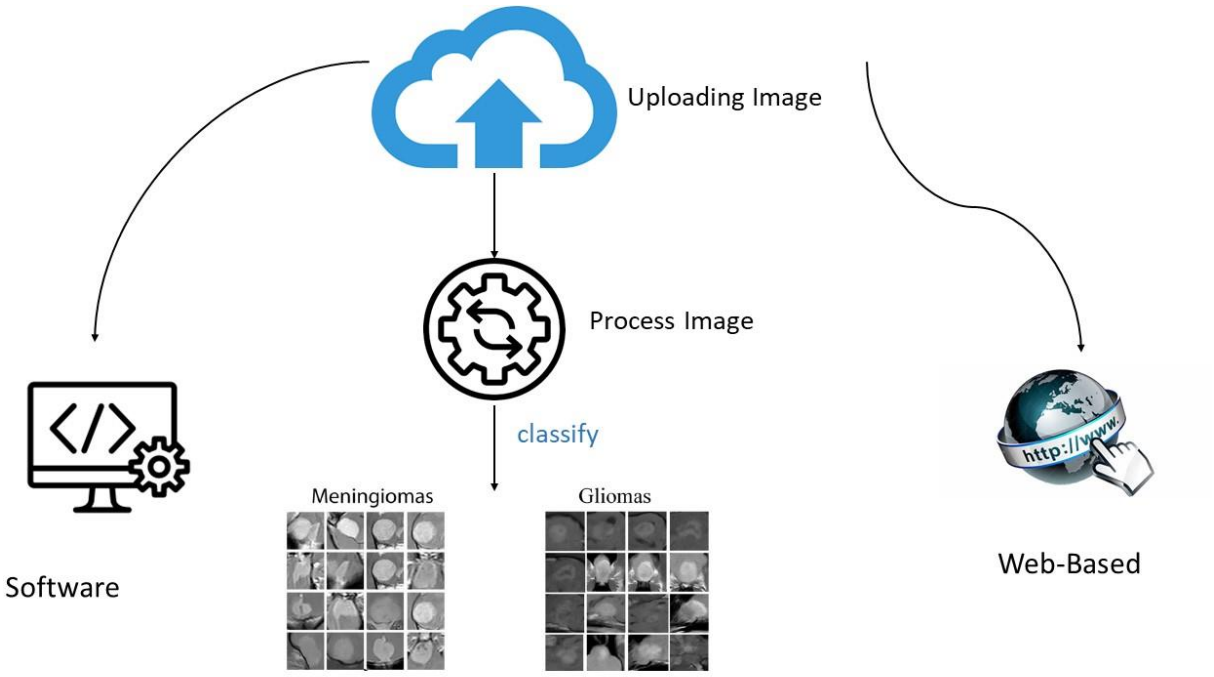

Figure 12 :This paradigm shows our suggested frame work for to distinguish between meningiomas and gliomas on canine MR-images

After finishing research part and implementation of network, it is easily for us to create our CAD. To this end- figure 12 shows our suggested framework which includes two types of CAD platform, first of all we propose our system will be used in some small clinic because of internet problem in some places in whole world. we will be create a software that is easily get MR image and get result the tumors type and this software can easily be updated in specific times by more accurate dataset . Our second system is web based application and vets could easily upload image and get assistance for types of option. After we get new images from web based and software our system be more accurate and reliable.

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