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Generative models for predicting chemical composition of gallstones

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Abstract. – OBJECTIVE: As we know, gallstones are a gallbladder disease with high incidence around the world. As the population has aged and living habits have changed, the incidence of the disease is increasing year by year. Gallstones are mainly classified into cholesterol, bile pigment and mixed type gallstones based on their chemical composition. Patients with different stone components have different treatment options. Therefore, it is very important to know the chemical type of the stone before treatment. Imaging examination is the main method to identify the components of gallstones in the body.

MATERIALS AND METHODS: Deep learning technology has an excellent data mining ability, and thus the combination of deep learning and medical treatment is always a research focus. In this work, we introduce a generative model to learn the features of the training data, to detect the composition of gallstones and to assist medical diagnosis. Furthermore, the theoretical analysis is given in detail.

RESULTS: The model could be used to determine the chemical composition of gallstones.

CONCLUSIONS: The potential of generative models in predicting the chemical composition of gallstones is shown in this study. In addition, theoretical analysis is also presented.

Key Words:
Auxiliary diagnosis, Composition of gallstones, Deep learning, Generative models, Generative adversarial network (GAN), Variational auto-encoder (VAE).

Introduction

Recently, generative models have become more important and popular because of their applicability in deep learning fields. They are crucial to many computer vision fields, such as treating images[1,2], and natural languages[3]. With the development of machine learning for big data[4-6], neural networks have great potential in medical field[7-10]. Of note, medical images denoising problem can be solved using the convolutional neural networks[11]. Recently, generative models were proposed to solve the medical images denoising problem and achieved significantly improved performance[12]. Generative models have the capability to represent complex data and the potential to solve problems, but the combination of the models and medicine have more enormous potential for growth because of the details, which are hard to guarantee to be realistic. Specifically, generative models are highly useful for predicting problems. In addition, generative models can be utilized to tackle various problems in the machine learning field, which is called semi-supervised learning[13]. However, their applications in medical fields need to be continuously extended.

Generative adversarial network (GAN)[14], one of the generative models, was proposed to solve the disadvantages of other generative models. Instead of maximizing the likelihood estimation and related strategies, GAN introduces the concept of adversarial learning between the generator G and the discriminator D. The network G and the network D act as adversaries for each other. The generator is a continuous, differentiable function mapping an arbitrary distribution from the latent space into the data space , which is used to fool the discriminator. The discriminator distinguishes where its inputs come from, the real data distribution or the generator. Generally, the network G and the network D are trained alternatively.

Gallstones are the most common gastrointestinal-related diseases in the world and have very

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high socioeconomic costs. According to statistics, some adults in developed countries suffer from gallstones. Gallstones are mainly classified into cholesterol stones, bile pigment stones, and mixed stones according to different cholesterol levels[15]. At present, research on the treatment of gallstones is gradually increasing. Non-surgical treatments such as dissolved stones and gravel have become important parts of the treatment of stones. The efficacy of non-surgical treatment depends largely on the type of calculus, which has led to a greater focus on the analysis of gallstone components, thereby improving the treatment of stones. The best treatment options are different depending on the composition of the stones. Cholesterol stones can be dissolved by ursodeoxycholic acid, but non-cholesterol stones cannot[16]. Equal-density cholesterol stones are extremely sensitive to extracorporeal shock wave lithotripsy, but this method has a poor effect on bile pigment stones[17].

The imaging methods for the diagnosis of gallstones are important. At present, the imaging methods used to analyse gallstone components include ultrasonic images, computed tomography (CT) and magnetic resonance imaging (MRI). To determine the chemical composition of gallstones, some researchers proposed a general convolution model to learn the characteristics of the collected imaging data[18]. Yao et al[19] presented a deep learning model for predicting chemical composition of gallstones and described the back-propagation strategy for training the convolutional neural network. Sawada et al[20] presented deep generative models for inorganic chemical compositions, namely, they generated chemical compositions without using crystal information by using deep learning methods and underlined the effectiveness of the Metropolis-Hasting-based (MH) atomic valency modification and the extrapolation performance, important for the arterial discovery. They constructed four types of generative models and proved that a conditional GAN (CondGAN) performs the best. Inspired by these papers, we used a deep generative model, which has a thread learning capacity, to learn the features of the training data to help predict gallstone components in this paper.

Related Work

Generative Methods

Formally, a generative model learns to model a real data probability distribution where the data exists in the d-dimensional real space . Most generative models are based on the maximum likelihood principle with a model parametrized by parameter . With independent and identically distributed (i.i.d.) training samples where , the likelihood is defined as the product of the probabilities that the model gives to each training data: where is the probability that the model assigns to . The maximum likelihood principle trains the model to maximize the likelihood that the model follows the real data distribution. From this point of view, we need to assume a certain form of explicitly to estimate the likelihood of the given data and retrieve the samples from the learned model after training. However, while the explicitly defined probability density function results in computational tractability, it may fail to represent the complexity of the real data distribution and learn the high-dimensional data distributions.

Nonlinear Processing

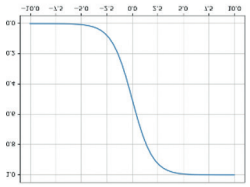
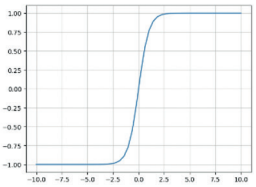
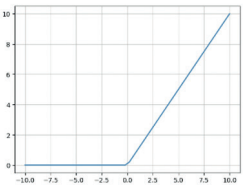
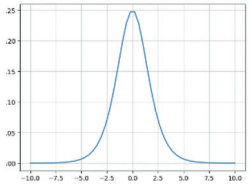
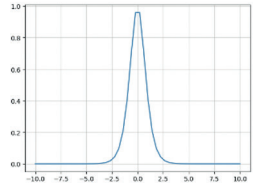
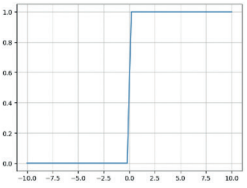
Convolutional neural network is essentially a linear function. The learning ability of neural networks would be weak if the entire network used only convolution operations. Therefore, it is necessary to increase the nonlinearity of the neural network by adding an activation function. Common activation functions include sigmoid function[21], tanh function[22], ReLU function[23], and the Leaky ReLU function[24], which is a variant of the ReLU function. The sigmoid function is also called the logistic function (threshold function). Its gradient is close to zero at and (Table I). Actually, the convolutional neural network updates the parameters through the chain rule during back-propagation and the network cannot be back-propagated, because of the vanishing gradient when the gradient approaches zero on the chain.

Models

Variational Auto-encoder

An autoencoder, one type of neural networks, is trained to copy the input to the output . Internally, it has a hidden layer that describes a code used to represent the input. The network includes two parts: an encoder function and a decoder function . They are used to produce a reconstruction signal . The architecture is presented in Figure 1. The autoencoder is not only utilized to simply learn to set everywhere. Generally, it is restricted

Table I. Three kinds of activate function.

	Sigmoid	Tanh	ReLU
Function Expressions	$f(x) = \frac{1}{1+e^{-x}}$	$Tanh = \frac{e^{x}-e^{-x}}{e^{x}+e^{-x}}$	$f(x) = \max(0, x)$
Function Curves			
Derivative Curves			

in ways that allow it to copy only approximately, and to copy only input that resembles the training data. The model is forced to prioritize which aspects of the input should be copied, so it often learns useful properties of the data. Traditionally, autoencoders have been used for dimensionality reduction or feature learning. Recently, theoretical connections between autoencoders and latent variable models have brought autoencoders to the forefront of generative modeling.

The variational autoencoder (VAE) is a directed model that can be trained purely with gradient-based methods. To generate a sample from the model, the VAE first draws a sample from the code distribution . The sample then runs with a differentiable generator network . Finally, is sampled from a distribution as follows:

$$p_{\text{model}}(x, g(z)) = p_{\text{model}}(x \mid z)$$

However, during training, the approximate inference network (or encoder) is used to obtain , and is then viewed as a decoder network.

The key insight behind variational autoencoders is that they may be trained by maximizing the variational lower bound associated with data point[25]:

$$\begin{aligned} L(q) &= E_{(z\sim(z|x)} \log p_{\text{model}}(z, x) + H((q(z|x)) \\ &= E_{(z\sim(z|x)} \log p_{\text{model}}(x|z) + D_{KL}(q(z|x) \| p_{\text{model}}(z)) \\ &\leq \log p_{\text{model}}(x) \end{aligned}$$

Generative Adversarial Network

GAN is a framework that applies adversarial learning to make realistic data. We simultaneously trained two models: the generator G and the discriminator D. G captures the data distribution of real-like fake samples from the latent variable , and D estimates the probability that its input comes from G or real data space. G and D compete with each other to achieve their individual goals, which is the called adversarial process[26]. This adversarial learning situation can be formulated as equation (1) with parameterized networks G and D. and in Equation (1) denote the real data probability distribution over data space X and the probability distribution of on the latent space Z, respectively.

$$\min_G \max_D V(G,D) = \min_G \max_D \left(E_{z\sim p_{data}(x)}[logD(x)] + E_{z\sim p_z(x|z)}[1 - logD(G(z))]\right)$$

V (G, D) is a cross entropy function that is commonly used in deep learning problems as the objective function. Note that G maps from Z into the element of X, and D takes an input and distinguishes whether x is a real sample or a fake sample generated by G[14].

The discriminator D wants to classify real or fake samples, V (G, D) is a common sigmoid cross entropy loss function in the binary classification problem. From G's perspective, G wants to deceive D as much as possible, so it tries to maximize the output when fake data that comes from

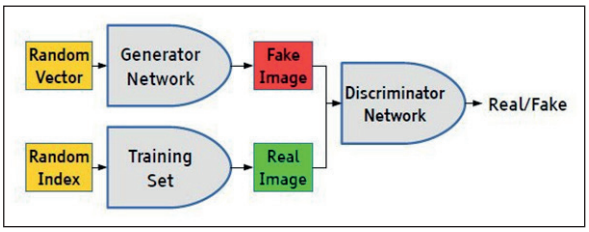


Figure 1. Generative Adversarial Network

the generator are presented to D. Consequently, D tries to maximize V (G, D) while G tries to minimize V (G, D), namely, the generator and discriminator are alternately trained. Figure 1 is an illustration of the GAN[14].

Ideally, the two functions G and D both have sufficient learning capacities, the relationship between G and D occurs when $p_{data}(x) = p_g(x)$ and D always equals ½ where $p_g(x)$ is the probability distribution of the fake data generated by the generator[14]. For the fixed G, the optimal discriminator is D^*.

$$D^* = \frac{p_g(x)}{p_g(x) + p_{data}(x)}$$

Discussion

Ultrasound Image

The automatic segmentation of ultrasound images is an important part of many applications, especially in the medical field[27,28]. Because ultrasound imaging has several advantages such as good real-time performance, relatively inexpensive costs, fast speed and convenience, it plays a vital role in the diagnosis of gallstones. Ultrasound imaging has been the accepted gold standard. The study found that ultrasound not only accurately determined the location, size, number, and echo intensity of stones, but also analyzed the composition of the stones. Cholesterol stones are a common type of stone of gallstones, and most of their typical sonograms are semicircular, crescent or round echoes. The cholesteric stones in the radial structure are characterized by strong echoes on the surface, gradually weakening towards the deep echoes, and finally becoming acoustic shadow, and also deepening the trailing edge of the stones. In addition, a "comet tail" appears. The sonogram of pigmented gallstones is characterized by a narrow and strong echogenic band, and the posterior attenuation is an acoustic shadow. The boundary is clear, or the whole stone is completely displayed, and the sound and shadow are weak. The contents of sterols and bile pigments in mixed stones are similar, and sometimes it is difficult to distinguish them from pure cholesterol stones or pure bile pigment stones. Ultrasound predicts cholesterol stones with a sensitivity up to 72.9%, and a specificity of 100%. The positive predictive value is 100%, and the negative predictive value is 93.4%[29]. The diagnostic accuracy of transabdominal ultrasound for common bile duct stones was 76.9%, the sensitivity was 76.2%, and the specificity was 81.3%[30]. Endoscopic ultrasonography (EUS) has important diagnostic value in patients with suspected choledocholithiasis and negative CT findings. The accuracy of EUS detection of common bile duct stones is 94.0% (sensitivity, 97.5%, specificity, 79.5%, positive predictive value, 95.2%, and negative predictive value, 88.6%)[31]. Therefore, using ultrasound images as the training data can improve the accuracy of predicting the chemical composition of gallstones and the diagnostic objectivity.

Computed Tomography

Computed tomography (CT) is extremely sensitive to the amounts of calcium within gallstones. The CT value of a stone is negatively correlated with the cholesterol content, and positively correlated with the calcium content of the stone. Moreover, a CT value < 140HU is regarded as a pure cholesterol stone[32]. In CT diagnosis, gallbladder stones are directly expressed as high- density or low-density stones. According to the different densities, gallbladder stones can be divided into the following classes: (1) high-density stones; (2) equal-density stones; or (3) low-density stones. The CT value is a unified unit that reflects the tissue density. The CT of water value is set to 0 HU, and the CT of bile value is set to 0-20 HU. Stones with the same density as bile cannot be visualized, so traditional CT scans cannot determine the presence of such stones. A CT value > 0 means that stones are low density stones, which are mostly high cholesterol stones. CT values in the range of 0-20 HU are constant density stones, which are mostly cholesterol stones. Stones with a CT value < 20 HU are high-density stones, most of which are gallstones[33]. Scholars have shown that cholesterol stones are amenable to adjuvant litholytic therapy[34,35]. The accurate classification of stones can guide the treatment of dissolved stones. Based on the characteristics of CT im-

ages, we use CT data to distinguish water-based bile and fat-containing gallstones, which helps to determine the stone composition.

Magnetic Resonance Image

Magnetic resonance imaging is extremely sensitive to changes in tissue composition. It can display more detailed gallstone structures, which may help to effectively determine the non-surgical treatment of gallstones, such as chemical dissolution and extracorporeal shock wave lithotripsy (ESWL)[36]. Depending on the composition, stones may experience soft tissue attenuation, near water attenuation, or surrounding calcified fat attenuation. Stones appear as signal voids in T2-weighted imaging. In T1-weighted imaging, cholesterol stones are usually iso- or hypointense, while pigment stones are hyperintense due to the presence of metal ions[37,38]. However, due to the high price of MR examinations, they are rarely used in the diagnosis of gallstones, and it is widely used in academic research.

Medical image big data analysis uses the original pixels of the medical image to capture the features of the image. In our methods, we can set the imaging features and the pathology of the diseased tissue as a priori information to train a generative adversarial network, with the minimum loss of function as the goal. In addition, the image feature information is statistically learned by the deep learning networks and the optimal model will be saved. New medical images, as the input of the optimal model, can more accurately predict the composition of gallstones, thus giving patients more precise treatment. In addition to imaging examinations, before making an imaging diagnosis using big data, we can first pre-treat the patients' corresponding symptoms and signs, as well as the risk factors associated with gallstones. This will further improve the prediction accuracy of gallstone compositions. The combination of human experts and machine assistance, such as in the presented deep learning model can obviously exceed the achievements of any single system.

Advantages and Disadvantages

For the GAN, there is no explicit representation of , and D must be synchronized well with G during training. The advantages are that only backpropagation, and not Markov chains, is used to obtain the gradients rather than, no inference is needed during learning processing, and a wide variety of functions can be incorporated into the model[15]. An adversarial process may also gain some statistical advantage from the generator network not being updated directly with data examples, and only with gradients obtained through the discriminator. Namely, the components of the input are not copied directly into the space of the generators' parameters. Another advantage is that the very sharp, even degenerate distributions can be represented by adversarial networks.

Algorithm 1. Minibatch stochastic gradient descent training of generative adversarial nets. The number of steps to apply to the discriminator, k, is a hyperparameter. We used $k = 1$, the least expensive option, in our experiments. An example for format for & While Loop in Algorithm.

1: **for** number of training iterations **do**
2: **for** k steps **do**
3: Sample minibatch of m noise samples $z^{(1)}, \cdots, z^{(m)}$ from noise prior $p_{g(z)}$.
4: Sample minibatch of m examples $x^{(1)}, \cdots, x^{(m)}$ from data generating distribution $p_{data}(x)$.
5: Update the discriminator by ascending its stochastic gradient:

$$\Delta_{\theta_d} \sum_{i=1}^{m} [logD(x^i) + \log(1 - D(G(z^i)))]$$

6: **end for**
7: Sample minibatch of m noise samples $z^{(1)}, \cdots, z^{(m}$ from noise prior $p_{g(z)}$.
8: Update the generator by descending its stochastic gradient:

$$\Delta_{\theta_d} \sum_{i=1}^{m} \log(1 - D(G(z^i)))$$

9: **end for**
10: The gradient-based updates can use any standard gradient-based learning rule. We used momentum in our experiments.

Conclusions

In this paper, a generative model, including VAE and GAN, is proposed to potentially learn features for the training of imaging data. Specially, the features learned from big medical data can potentially be used to analyses the chemical composition of gallstones to determine the treatment options. Furthermore, the theoretical analysis is given in detail. Finally, we analyses how the model helps to determine the chemical composition of gallstones. In the future, we plan to insert more effective generative models into the neural network framework to further enhance its predictive ability.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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