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Analysis of Risk Factors for Diabetic Retinopathy and the Role and Mechanisms of Melatonin

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Abstract: Diabetic retinopathy is a common micro vascular complication of diabetes and the leading cause of blindness in working-age people. Oxidative damage is an important mechanism leading to diabetic retinopathy, and inflammatory response also plays an important role in its development. Furthermore, one of the hallmarks of diabetic retinopathy is impaired autophagy. Melatonin is a molecule with powerful antioxidant effects. It also has significant anti-inflammatory effects and can inhibit the expression of a variety of inflammatory factors. The eyes are one of the key sites for melatonin secretion, and eye tissue is the main place where melatonin plays its role. Melatonin has been shown to have neuroprotective effects in experimental and clinical models of several eye diseases. Systematic evaluation of risk factors for diabetic retinopathy in patients with diabetes provides a scientific basis for effective clinical prevention and treatment. Relevant studies were summarized on risk factors for patients with diabetes, and literature screening, data extraction, and quality assessment were performed.

Keywords: Diabetic Retinopathy; Melatonin; Risk Factors; Analysis
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1. Current Status of Research on Diabetic Retinopathy

Diabetic retinopathy is a common eye complication caused by diabetes and the leading cause of blindness among working-age people in developed countries, placing a heavy burden on society and families. In the early stage of the disease, patients have no conscious symptoms, and the lesion involves the macular area before varying degrees of vision loss[1]. Diabetic retinopathy has long been considered a microvascular disease[2]. The pathogenesis of diabetic retinopathy is complex and involves multiple cell signaling pathways, including polyol pathway, protein kinase C activation, glycosylation end product accumulation, and amino-hexose pathway[3]. Hyperglycemia is a major risk factor for diabetic retinopathy. In the hyperglycemic environment, the activity of proinflammatory cytokines, chemokines and adhesion molecules in the retina increases, which promotes the adhesion of white blood cells in the blood vessel wall, This leads to the destruction of the blood-retinal barrier and apoptosis of vascular endothelial cells, thus initiating an inflammatory cascade in the retina[4]. Vascular endothelial growth factor is a key factor in the progression of proliferative diabetic retinopathy and diabetic macular edema. Retinal ischemia/hypoxia leads to up-regulation of VEGF through activation of hypoxia-inducing factor 1. High glucose levels reduce the activity of antioxidant enzymes in retinal cells, such as superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase[5]. Mitochondrial electron transport chain dysfunction, abnormal loss of electrons in

electron transport chain complexes I and III, resulting in elevated levels of reactive oxygen species. Increased levels of reactive oxygen species (ROS) can induce excessive cellular autophagy, leading to cell damage. Especially in the state of starvation, H2O2 induces autophagy, resulting in apoptosis and necrosis of capillary endothelial cells, causing vascular damage, and eventually diabetic retinopathy[6].

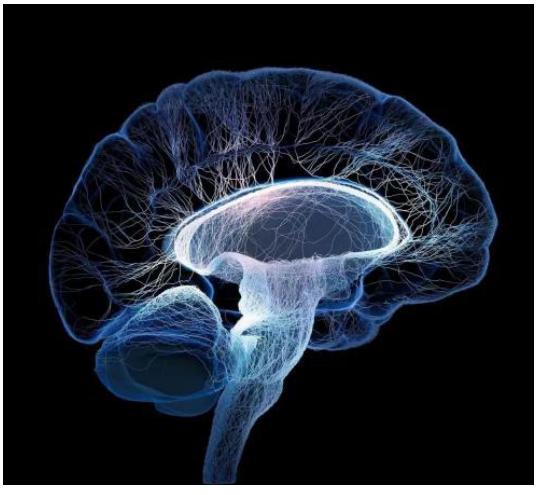
At present, the main treatments for diabetic retinopathy are retinal photocoagulation and vitrectomy, but not all patients are effective, and only in the advanced stage of the disease[7]. Anti-VEGF therapy has shown significant clinical benefit in patients with diabetic retinopathy, but most patients fail to achieve significant visual improvement.[8]. Due to the short half-life of anti-VEGF agents, it is necessary to inject once every month or every 2 months to ensure efficacy. Frequent injections may increase the incidence of endophthalmitis[9]. Economic burden and poor patient compliance also limit the use of anti-VEGF drugs in clinical practice. In addition, the use of large doses of anti-VEGF drugs may cause retinal degeneration and gliosis[10]. Moreover, high-throughput RNA sequencing analysis showed that VEGF antagonism could activate retinal degeneration, inflammation and other adverse reactions. Therefore, the treatment of diabetic retinopathy remains challenging, and the development of drugs targeting its pathogenesis is a key issue that needs to be addressed urgently.

2. Introduction of Melatonin

Melatonin is a neurohormone present in almost all forms of life, mainly regulating sleep and seasonal behavior in vertebrates[11]. In addition to regulating the sleep-wake cycle in humans, melatonin also plays an important role in antioxidant defense, maintaining mitochondrial homeostasis and reducing inflammatory responses[12]. Melatonin is a highly effective endogenous antioxidant. The high antioxidant effect of melatonin is partly attributed to its small molecular size and lipophilicity and hydrophilicity, which enable it to easily pass through all biological barriers and thus act efficiently at the cellular and mitochondrial levels[13]. Although most melatonin is secreted by the pineal gland, melatonin is also synthesized in many tissues outside the pineal gland, such as the retinal photoreceptors, ciliary body, and lens in the eye[14]. The biological functions of melatonin are associated with two members of the G protein-coupled receptor family, MT1 and MT2, which are expressed in mammalian retinal photoreceptors, retinal horizontal cells, corneal epithelium, stromal endothelium, and sclera[15]. Studies have shown that melatonin protects the eye by inhibiting inflammatory factors, resisting oxidative stress, regulating endoplasmic reticulum stress and autophagy.Studies have shown that melatonin has neuroprotective effects in experimental and clinical models of various eye diseases.

The pineal gland, also known as the posterior pituitary gland, is a small endocrine gland in the human body. It is located between the anterior hypothalamus and thalamus in the diencephalon.It is a reddish-brown bean-shaped body that resembles a pine cone. Although the pineal gland is very small, it has the functions of secreting melatonin, forming the biological clock, inhibiting precocious puberty and regulating immunity. The secretion of melatonin is affected by light. The dimmer the light, the more melatonin the pineal gland secretes. Melatonin plays an important role in regulating the biological clock, sleep cycle and seasonal physiological activities.Figure 1 is a diagram of the structure of the pineal gland.

Figure 1: The pineal gland secretes melatonin



3. Melatonin Inhibits Inflammation

Inflammation is a "double-edged sword" and a host defense response to tissue damage. It promotes homeostasis in the short term, but if triggered improperly, especially when chronically activated, inflammation can be harmful and promote the progression of multiple diseases, such as diabetic retinopathy. Inflammation plays an important role in the development and progression of diabetic retinopathy. The release of proinflammatory cytokines and the stasis of leukocytes in retinal capillaries are the initial events in the development of diabetic retinopathy. This effect is mediated by the synergistic action of multiple inflammatory mediators and transcription factors, such as cytokines and chemokines, including interleukin 6 (IL-6), factors such as IL-8, IL-1β, and tumor necrosis factor α, the complement system, and nuclear factor κB are closely associated with inflammation. In addition to being a direct antioxidant, melatonin can also reduce inflammation and oxidative stress in the retina through receptor-mediated signaling. Melatonin inhibits the production of proinflammatory cytokines and proteins, including IL-1β, TNF-α, and inducible nitric oxide synthase (iNOS), through the NF-κB pathway, which has a strong protective effect on melatonin[16]. Hyperglycemia-induced oxidative stress and pro-angiogenic factors like VEGF play a crucial role in the onset and progression of diabetic retinopathy. Melatonin has been shown to suppress the levels of VEGF, intercellular adhesion molecule-1, matrix metalloproteinase 2, and MMP9 that are elevated due to high glucose and IL-1β exposure, thereby inhibiting the inflammatory response and angiogenesis, which has potential therapeutic value for melatonin. However, there is no direct evidence available for the potential mechanism through which melatonin reduces VEGF expression. Studies have shown that melatonin can prevent the activation of p38 MAPK through different stimuli (including TNF-α, IL-1β, and oxidative stress), thereby improving various inflammatory conditions and reducing cell apoptosis[17]. Hyperglycemia can generate ROS through mechanisms such as mitochondrial dysfunction, unstable glycosylation, glucose autooxidation, and intracellular polyol pathways. ROS has the capacity to activate numerous genes responsible for controlling inflammatory signaling pathways, thus triggering and enhancing the inflammatory reactions. These genes may be upregulated by ROS-mediated NF-κB activation, which in turn regulates a variety of enzyme genes, including iNOS, cyclooxygenase 2, and proinflammatory cytokines[18]. The secretion of melatonin has the capability to curtail the escape of electrons within the mitochondrial electron transport system, which in turn diminishes the conversion of oxygen into superoxide anion radicals. Consequently, melatonin exhibits a distinct safeguarding influence on the emergence and progression of related conditions.

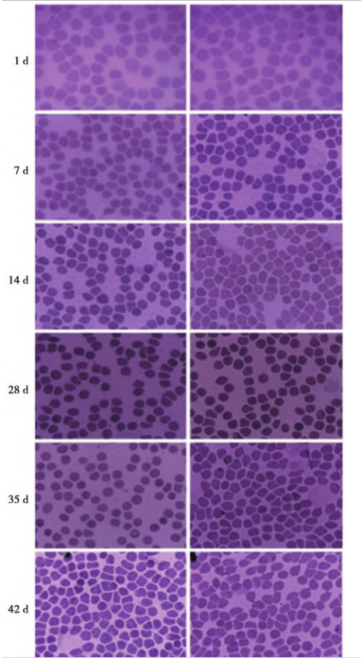
4. Melatonin's Antioxidant Effects

Within the context of diabetes, there is a notable surge in the concentration of diverse inflammatory markers within cellular structures, accompanied by a disrupted equilibrium between the oxidative and antioxidative mechanisms, along with an imbalance in the synthesis and elimination of inflammatory agents throughout the organism. Cell signaling pathways that are sensitive to oxidative stress and inflammation will be activated and further generate activity. Reactive oxygen species and pro-inflammatory elements induce a multitude of pathophysiological alterations. In the retinas of rats with diabetes, the expression of glutathione and gamma-glutamylcysteine synthetase is diminished. GCC is the key enzyme responsible for the synthesis of glutathione. Injection of MT can increase GCL levels through Akt phosphorylation, thereby increasing the activity of Nrf2. Relevant studies have shown that melatonin can reduce glutathione redox status and stimulate antioxidant enzymes (including glutathione reductase, glutathione peroxidase, superoxide dismutase) by reducing serum hydroxyl free radicals. The substances such as enzymes and catalase are utilized to attain the reduction of oxidative stress. Melatonin mitigates oxidative stress by modulating the PI3K/Akt-Nrf2 signaling route. Triggering this pathway can increase the production of other antioxidants and reduce inflammation by inhibiting the NF-KB activation cascade, thereby regulating neuroinflammation and playing a role in diabetic neuropathy. Neuro properties. Moreover, the administration of melatonin averted the diabetes-related decline in SOD mRNA levels and the surge in caspase-3 mRNA levels, contributing positively to the inhibition of retinal neuron apoptosis. Concurrently, the levels of vasoactive cytokines including hypoxia-inducible factor-1α, VEGF-A, and pigment epithelium-derived factor were diminished following melatonin therapy, exerting a therapeutic impact on the vascular complications associated with diabetes[19]. In individuals with diabetic retinopathy, there is an elevated level of nitric acid stress. This leads to an enhancement of NO levels due to the heightened expression of iNOS, culminating in the creation of peroxynitrite. Subsequently, peroxynitrite undergoes breakdown via lipid peroxidation, yielding

malondialdehyde as a byproduct. In the retina of prediabetic rats, melatonin can reduce lipid peroxidation, NOS activity and NO production levels, and furthermore, it impedes the decline in catalase activity within the retina, enabling the effective neutralization of hydrogen peroxide and obstructing the generation of hydroxyl free radicals. At the same time, melatonin and its metabolites have anti-lipid peroxidation effects and can stabilize cell membranes against free radical attacks.

Melatonin also neutralizes highly reactive hydroxyl radicals such as singlet oxygen, hydrogen peroxide, and peroxynitrite anions, which play a major role in lipid peroxidation during diabetes. Upon engaging with free radicals, melatonin activates a chain of neutralization by transforming into non-reversible and robust breakdown products that possess radical-trapping abilities[20]. In the context of diabetes, the reactive changes in retinal glial cells mark an incipient pathological process. Researchers have investigated the impact of melatonin on the activation and lipid peroxidative damage of these glial cells in rodent models with diabetes. They propose that melatonin has the potential to inhibit gliotic reactivity and diminish the buildup of malondialdehyde, thereby mitigating oxidative neuronal toxicity. Additionally, melatonin is found to decrease the edema in the processes of Müller cells and the terminal processes of astrocytes, as well as to lower VEGF concentrations, nitric oxide synthesis, and vascular permeability in the retinas of rats exposed to hypoxia[21]. Within the context of diabetic retinal pathology, the mitochondria suffer a fate of impairment, stemming from the migration of the pro-apoptotic factor Bax from the cell's cytoplasm into its mitochondrial matrix, accompanied by the escape of cytochrome c from these organelles. The blockage of superoxide radicals can prevent the glucose-evoked malfunction of mitochondria, the activation of caspase-3, and the demise of retinal capillary cells. Melatonin, renowned for its potent antioxidant properties, has the potential to impede the progression of diabetic retinopathy by preventing the build-up of DNA altered by oxidative stress and nitrotyrosine, as well as the apoptosis of capillary cells in the retina; however, additional confirmation through research is required. The processes of mitochondrial division and amalgamation are governed by the nutritional condition of the cells[22]. In scenarios of elevated blood glucose levels, there is an upsurge in the manifestation of proteins responsible for mitochondrial division, whereas a decline is observed in the manifestation of proteins that facilitate mitochondrial merging. Additionally, such cells exhibiting hyperglycemia demonstrate a diminished calcium content within their mitochondria, concurrently exhibiting an augmented calcium concentration in the cytoplasm. Melatonin has the capability to thwart the alterations in mitochondrial dynamics, specifically fission and fusion, as well as the fluctuations in mitochondrial calcium concentrations that are triggered by elevated glucose levels. This action aids in guarding against the neural retinal and retinal microvascular harm caused by streptozotocin (STZ)[23]. The illustration in Figure 2 depicts the influence of melatonin on the oxygen transport capacity and the oxidative stress status within red blood cells throughout the preservation phase[24].

Figure 2: Morphology of RBCs in two groups at different storage times



5. Melatonin Inhibits Endoplasmic Reticulum Stress and Regulates Autophagy

The endoplasmic reticulum serves as a pivotal site for a spectrum of cellular activities, managing lipid synthesis, calcium regulation, and maintaining protein equilibrium. When subjected to adverse conditions, the integrity of the ER is undermined, disrupting the process of protein assembly and causing an accumulation of improperly folded proteins. This triggers a distinctive cellular defense mechanism known as the unfolded protein response. This response is designed to shield cells from harm and restore internal balance, but during extended periods of ER strain, it can instead stimulate apoptosis. Stressors affecting the ER can also modulate autophagy, which has the dual capacity to either promote cell survival or contribute to cell demise, contingent upon the context. The leakage of altered low-density lipoprotein has been linked to the degeneration of pericytes, a nascent sign of diabetic retinopathy. Additional evidence from in vitro experiments, animal models, and clinical observations suggests that this modified form of low-density lipoprotein not only initiates oxidative stress but also exacerbates ER stress, contributing to pericyte attrition in the context of diabetic retinopathy[24]. Another deleterious effect of modified low-density lipoprotein is the induction of apoptosis of retinal pigment epithelial cells through oxidative stress, ER stress, and autophagy. Elevated glucose levels have the capacity to trigger autophagic activity within retinal Müller cells. Nevertheless, the impairment of lysosomal function results in the build-up of autophagosomes within the cell cytoplasm, which consequently prompts an overproduction of VEGF and triggers apoptosis. The role of autophagy in diabetic retinopathy is multifaceted: it serves a protective function against the stress caused by moderately oxidized glycated low-density lipoprotein, yet it facilitates cell demise when faced with more intense stressors. Melatonin has the ability to diminish the expression of genes and proteins related to endoplasmic reticulum (ER) stress in a manner proportional to its concentration, effectively mitigating the ER stress caused by methamphetamine and safeguarding against glial cell death. Additionally, melatonin can be utilized in conjunction with 4-phenylbutyrate, an ER stress modulator, to lessen glucotoxicity in type 2 diabetes and to prevent cerebral ischemia/reperfusion injury by suppressing ER stress-mediated autophagy[25]. Despite these findings, concrete evidence regarding melatonin's role in diabetic retinopathy through the attenuation of ER stress and the regulation of autophagy is not available, necessitating additional research to elucidate the intricate regulatory pathways of melatonin concerning retinal autophagy and ER stress in the context of diabetic retinopathy.

6. Exploration of Melatonin's Function and Operation in the Context of Diabetic Retinopathy

This compound is capable of mitigating the harm resultant from inflammation and oxidative strain associated with diabetic retinopathy, owing to its robust anti-inflammatory and antioxidative properties. Melatonin has the ability to suppress the gliotic response of Müller cells induced by hyperglycemia, as well as the secretion of VEGF, thereby slowing the progression of diabetic retinopathy. Additionally, melatonin aids in alleviating endoplasmic reticulum distress and modulating autophagy, contributing to the preservation of pericytes and retinal pigment epithelial cells within the diabetic retinopathic environment. These research results show that melatonin can play a preventive and therapeutic role in diabetic retinopathy and become an effective drug against diabetic retinopathy. However, there are still some problems in the application of melatonin drugs, such as limited bioavailability of oral medication, short plasma half-life and low subtype receptor selectivity[26]. Consequently, it is of utmost significance to investigate and advance melatonin and its derivatives that exhibit enhanced metabolic stability, greater specificity for subtypes, and a reduced occurrence of adverse reactions. A plethora of recent patent submissions involving melatonin pertain to sleep disturbances and/or disorders linked to circadian rhythms. The efficacy of diabetic retinopathy and eye diseases requires a more detailed description to clarify all the properties of such melatonin analogs[27].

7. Analysis of Risk Factors for Diabetic Retinopathy

In the realm of data preparation, we employ techniques such as handling missing data, conducting outlier examination, and converting data formats on the assembled dataset. In the domain of addressing missing data, we categorize the absent values into three distinct groups: those that are left unaltered, those that require imputation, and those that necessitate removal. We meticulously handle each of these missing data categories; in the sphere of outlier examination, we've developed a wavelet-based technique for detecting irregularities in numerical datasets. Analyzing the frequency-based signal shifts for each metric,

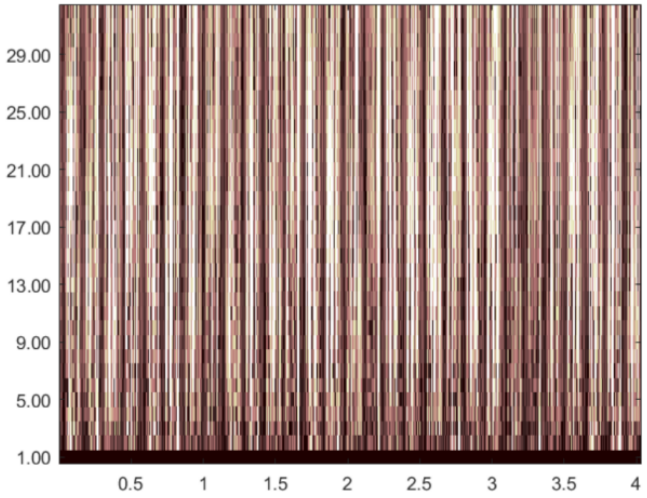
we deduce that the metric data is devoid of outliers, remaining within the expected range; for the aspect of data format transformation, we apply a numeric replacement strategy to convert categorical text data into numerical equivalents.

Table 1 Explanation of symbols

Symbol	Significance
d_f	Width adjustment coefficient
C_j	The core unit of the jth node within the concealed tier
D_j	The breadth indicator of the jth unit in the concealed tier
w_{kj}	The modification factor connecting the kth node of the exterior tier to the jth node in the concealed tier
$w_{kj}(t)$	The tuning factor between the kth output node and the jth concealed tier node at the t-th cycle
$c_{ji}(t)$	The focal element of the jth concealed tier node corresponding to the ith input node during the t iteration computation
$d_{ji}(t)$	Width corresponding to center $c_{ji}(t)$
η	Learning factor
O_{lk}	Anticipated yield of the k-th output unit for the initial input instance
y_{lk}	Computed response of the k-th output unit upon the first input example

We first discussed the factors affecting retinopathy in diabetic patients, and summarized 6 influencing factors. A weighted feature selection model based on random forest was constructed, and the CART decision tree of random forest was used as a weak learner to obtain the feature values of each factor, and finally the main factors affecting retinopathy in diabetic patients were identified.Based on the wavelet outlier analysis method, the abnormal isolated points of the indicators are solved, and the results are shown in Figure 3.The horizontal axis is time and the vertical axis is scale.

Figure 3: Continuous wavelet solution results



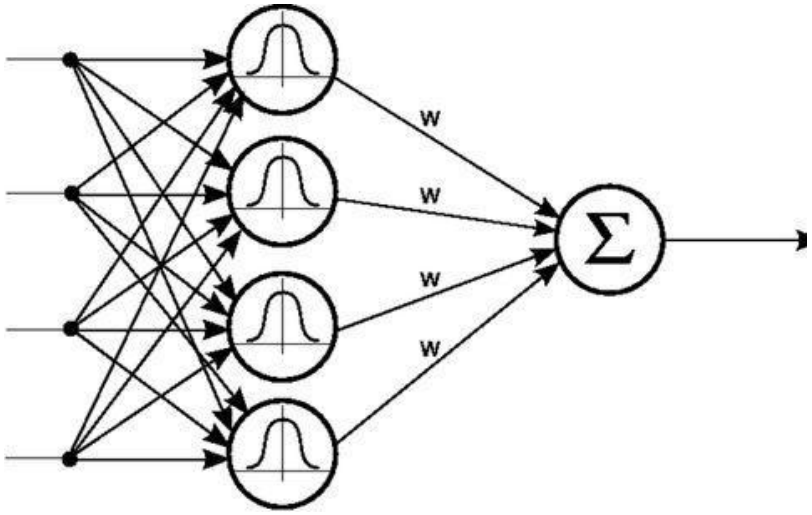
Upon examining the outcomes derived from wavelet analysis and noting the shifts in frequency patterns across diverse metrics, it is ascertainable that the metric data lacks any extraordinary isolated occurrences, thereby confirming that the dataset falls within acceptable parameters.

The RBF network constitutes a forward architecture with three distinct strata, featuring a solitary concealed tier. The initial stratum serves as the reception layer, comprising nodes that receive input signals. The intermediary layer is the tier, whose node count is dictated by the specific requirements of the problem at hand. The neurons within this hidden tier utilize a transformational function known as the radial basis function, which is characterized by its radial symmetry, non-negativity, and linear attenuation towards a central point, making it a localized response mechanism. The uniqueness of this local responsiveness is evident in the distinct manner in which the input layer's signals are transformed into the hidden layer's

signals, differing from the global response functions found in other network architectures. The terminal layer is the emission layer, responsible for generating a response to the input pattern. The role of the input layer is solely to convey signals, and the links between it and the hidden layer can be perceived as having a unity connection weight. Since the output and hidden layers have disparate functions, their learning methodologies also differ. The emission layer modifies linear weights and employs a linear optimization approach, resulting in rapid learning; conversely, the hidden layer modifies the parameters of its activation function, such as the Green function or typically the Gaussian function, and adopts a nonlinear optimization method[28].

Illustrated in figure 4, the core concept of the RBF neural network revolves around employing RBF as the foundation for the hidden unit's structure, thus creating the hidden layer's space. This hidden layer then processes the input vector, effectively converting the input data from a low-dimensional format to a high-dimensional one. This transformation enables the resolution of linearly inseparable issues that exist in the low-dimensional realm by allowing them to be solved linearly within the high-dimensional space. To elaborate, the fundamental "base" of the RBF hidden unit is integral in shaping the hidden layer's space, facilitating a direct mapping of the input vector into this space. Once the center of the RBF is fixed, the mapping correlation is established. The transition from the hidden layer's space to the output space follows a linear pattern, meaning the network's output is a linear combination of the unit outputs, with the weights in this context being the network's tunable parameters.

Figure 4: Principle of RBF neural network



Radial Basis Function network instruction: the objective of this instruction process is to ascertain the ultimate synaptic weights for both hidden and output layers.

The instructional phase is segmented into a dual-stage approach: initially, an unsupervised method is employed where the system ascertains the synaptic weights connecting the input neurons to the concealed layer nodes; subsequently, a supervised technique is utilized to refine and establish the synaptic strength between the concealed layer and the terminal layer[29].

Prior to commencing the training process, it is necessary to furnish the input vector designated as X, the matching target output vector referred to as Y, along with the dimension vector for the radial basis function's width. When inputting samples (l=1,2,..., N) for training for the first time, the expression and calculation method of each parameter are as follows:

(1) Determine parameters

Determine input vector X

$$X = [x_1, x_2, \ldots, x_n]^T$$

Where: n is the number of input layer cells.

Ascertain the resultant vector Y and the objective output vector O.

$$Y = [y_1, y_2, \ldots, y_q]^T$$

$$O = [o_1, o_2, \ldots, o_q]^T$$

Where: q is the number of output layer units.

Commence by setting the synaptic weight values between the concealed layer and the terminal layer.

$$W_k = \left[w_{k1}, w_{k2}, \ldots, w_{kp}\right]^T, (k = 1,2,\ldots,q)$$

Location: p signifies the count of neurons within the concealed layer, while q denotes the total neurons in the output layer.

The specified centroid-based approach dictates the technique for initializing the weights connecting the hidden layer to the output layer:

$$W_{kj} = \min k + j\frac{\max k - \text{mink}}{q+1}$$

The location in question pertains to the minimum value, denoted as 'mink', pertaining to the anticipated outputs across all neurons of the kth variety within the training dataset. Conversely, 'Maxk' represents the highest value among the expected outcomes for the aforementioned kth neuron in the training dataset.

Subsequently, the core parameters of the neurons situated within the concealed layer are initialized.

$$c_j = \left[c_{j1}, c_{j2}, \ldots, c_{jn}\right]^T$$

The center of neurons in different hidden layers should have different values, and the corresponding width with the center can be adjusted, so that different input information features can be reflected by different hidden layer neurons to the greatest extent. In practical applications, an input information is always included in a certain value range. Without losing generality, the initial value of the central component of each neuron in the hidden layer is changed from small to large at equal intervals, so that weak input information can generate strong response near the smaller center. The proximity can be fine-tuned through the variation in the count of neurons situated within the concealed layer. The benefit lies in our ability to pinpoint a more logical quantity of neurons in the hidden layer through a process of experimentation and adjustment, thereby ensuring the initialization of the centroid is as judicious as can be. Different input characteristics are more clearly reflected in different centers, reflecting the characteristics of the Gaussian kernel.

Taking into account the aforementioned four elements, the starting values for the core parameters within the RBF neural network are established as follows:

$$c_{ij} = \min i + \frac{\max i - \min i}{2p} + (j-1)\frac{\max i - \min i}{p}$$

Where: p represents the aggregate count of nerve cells within the concealed layer, with j ranging from 1 to p; Mini denotes the lowest data point among all input values for the ith characteristic within the educational dataset, whereas Maxi stands for the highest data point for the ith characteristic in the same dataset.Commence the width vector initialization.

$$D_j = \left[d_{j1}, d_{j2}, \ldots, d_{jn}\right]$$

The dimension of the width vector has a direct impact on the operational scope of neurons with respect to incoming data: a reduced width results in a constricted action function for the neurons within the associated hidden layer, thus diminishing the sensitivity of neighboring information centered around other neurons to the influence of this particular neuron. Computation approach:

$$d_{ji} = d_f\sqrt{\frac{1}{N}\sum_{k=1}^{N}\left(x_i^k - c_{ji}\right)}$$

Among them, d_f is the width adjustment coefficient, which is less than 1. Its function is to make each hidden layer neuron more easily realize the perception of local information, which is conducive to improving the local response ability of RBF neural network.

(2) Determination of transfer parameters of radial basis function neural network

The transfer function of RBF network takes the distance $\left|X - C_j\right|$ between the input vector and the threshold vector as the independent variable. The resultant value is derived from the multiplication of the input vector with the row vector derived from the weighting matrix C. The adjustable parameters within the RBF neural network can manifest in various configurations. Typically observed forms include:

Gaussian function

$$\phi_i(t) = e^{-\frac{t^2}{\delta_i^2}}$$

Reflected sigmoid function (abnormal S type function)

$$\phi_i(t) = \frac{1}{e^{\frac{t^2}{\sigma^2}}}$$

Inverse Multiquadric function (inverse distortion correction function)

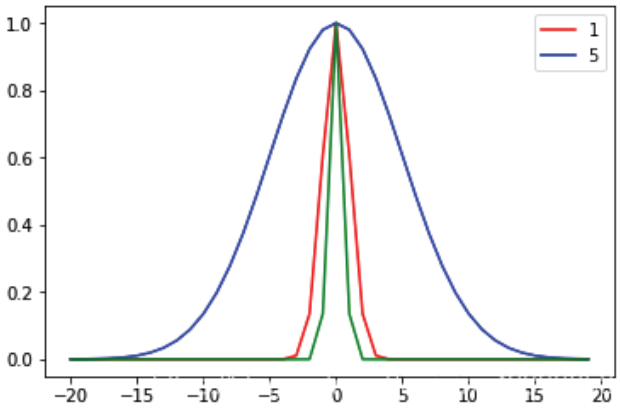
$$\phi_i(t) = \frac{1}{\left(t^2 + \delta_i^2\right)}, a > 0$$

The Gaussian function is more commonly used. This paper uses the Gaussian function

$$y = e^{-x^2}$$

As shown in Figure 5,when the input argument is 0, the transfer function gets the maximum value of 1. When the proximity between the mass and the input vector diminishes, the yield of the network escalates. Put another way, the radial basis function reacts to the input stimulus in a localized manner. Should the input stimulus X falls within the central scope of the function, the hidden layer node generates a significant output. It is evident that this network possesses the characteristic of localized approximation.

Figure 5: Principle of Gaussian radial basis function



Upon introducing the input vector to the network's entry point, every radial basis unit computes a signal that quantifies the proximity of the input vector to its respective weight vector. Should there be a significant discrepancy between the input vector and the weight vector, the radial basis function's yield hovers around zero. Conversely, when the input vector aligns closely with the weight vector, the radial basis layer's response approaches unity, mirroring the weight magnitude of the subsequent layer (the concealed layer) post its transmission through the linear neuron in that layer. During this sequence, if a solitary RBF neuron yields a value of 1, with all other neurons emitting 0 or near 0, the linear neuron's output equates to the weight value of the hidden layer tied to the neuron that produced the output of 1.

Calculate the output value z_j of the j th neuron in the hidden layer

$$z_j = \exp\left(-\left|\frac{X - C_j}{D_j}\right|^2\right), j = 1,2,\ldots,p$$

Where: C_j is the central vector of the jth neuron in the hidden layer, which is composed of the central components of the jth neuron in the hidden layer corresponding to all neurons in the input layer, $C_j = \left[c_{j1}, c_{j2}, \ldots, c_{jn}\right]^T$; D_j is the width vector of the jth neuron in the hidden layer, corresponding to, $D_j = \left[d_{j1}, d_{j2}, \ldots, d_{jn}\right]^T$, The larger the D_j. The influence range of hidden layer on input vector is larger, and the smoothness between neurons is better; | |is a European norm.

(4) Calculate the output of output layer neurons

$$Y = \left[y_1, y_2, \ldots, y_n\right]^T$$

$$y_k = \sum_{j=1}^{p} w_{kj} z_j, k = 1,2,\ldots,q$$

Wherein, w_{kj} is the adjustment weight between the k-th neuron in the output layer and the jth neuron in the hidden layer.

(5) Iterative calculation of weight parameters

The approach employed for optimizing the weight parameters of the RBF neural network is the gradient descent algorithm. By means of iterative learning, the parameters for the center, the spread, and the tuning weights are refined to their optimal values, with the computational process outlined as follows:

$$w_{kj}(t) = w_{kj}(y-1) - \eta \frac{\partial E}{\partial w_{kj}(t-1)} + \alpha \left[w_{kj}(t-1) - w_{kj}(t-2) \right]$$

$$c_{ji}(t) = c_{ji}(t-1) - \eta \frac{\partial E}{\partial c_{ji}(t-1)} + \alpha \left[c_{ji}(t-1) - c_{ji}(t-2) \right]$$

$$d_{ji}(t) = d_{ji}(t-1) - \eta \frac{\partial E}{\partial d_{ji}(t-1)} + \alpha \left[d_{ji}(t-1) - d_{ji}(t-2) \right]$$

Where: $w_{kj}(t)$ is the adjustment weight between the kth output neuron and the jth hidden layer neuron in the calculation of the th iteration; $c_{ji}(t)$ is the central component of the j hidden layer neuron for the i input neuron in the t iteration calculation; $d_{ji}(t)$ is the width corresponding to the center $c_{ji}(t)$; η is the learning factor.

E is the RBF neural network evaluation function:

$$E = \frac{1}{2} \sum_{l=1}^{N} \sum_{k=1}^{q} \left(y_{lk} - O_{lk} \right)^2$$

Wherein: O_{lk} is the expected output value of the kth output neuron at the first input sample; y_{lk} is the network output value of the k-th output neuron at the first input sample.

To sum up, the learning algorithm of RBF neural network is given:

The neural network parameters are initialized according to the five steps of determining the parameters, and the values of η and α and the value of iteration termination precision ε are given.

Calculate the value of root mean square error RMS of network output according to the following formula. If $RMS \leq \varepsilon$, the training is over, otherwise go to step

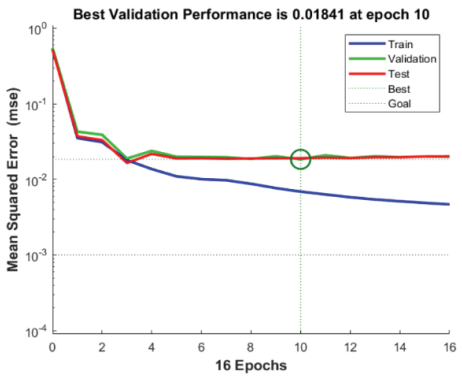
$$RMS = \sqrt{\frac{\sum_{i=1}^{N} \sum_{k=1}^{q} (O_{lk} - y_{lk})^2}{qN}}$$

According to iterative calculation of weight, the adjustment weight, center and width parameters are calculated iteratively.

8. Model Solving and Simulation

We've modified the architecture by adjusting the input layer to consist of 6 neurons, the output layer to have a single neuron, and increasing the hidden layer to 10 neurons. For the dataset, we've allocated 80% of the total attached samples for training purposes, with the remaining 20% designated for validation. The performance metrics for the RBF neural network, following training and validation, can be observed in the subsequent graphical representation, depicted as figure 6.

Figure 6: RBF neural network training results



Following the analysis of the neural network's training outcomes, it has been determined that the network's training accuracy amounts to a margin of error of 0.018. Subsequently, the test dataset was utilized to validate the network's predictive capabilities, yielding a discrepancy of 0.024 between the forecasted outcomes and the actual values.

9. Improved RBF Neural Network Based on PSO

The primary goal of training the BF network is to address a set of issues by employing its training algorithms, which include determining the count of neurons in the hidden layer, identifying the central points of these hidden neurons, establishing the breadth parameters for the radial basis functions, and ascertaining the connection weights between the hidden layer and the output layer. By substituting conventional methods with intelligent optimization techniques, the aim is to discover the ideal parameters for the RBF network model via a process of education and drill. This encompasses the quantity of hidden layer neurons, the centroids of the hidden layer neurons, the parameters dictating the width of the radial basis functions, and the synaptic weights linking the hidden layer to the output layer. The utilization of the particle swarm optimization algorithm to refine RBF networks entails the following steps:

(1) Determine the structure of the RBF network

Establish the architecture of the RBF neural network by identifying the count of neurons in the input, hidden, and output layers. The neuron count in the input and output layers should be derived from the specific input-output correlation of the issue at hand. The methodology for ascertaining the quantity of central neurons within the hidden layer is delineated below.

$$h = m(n+1)$$

Within this context: 'h' denotes the quantity of nodes present in the concealed layer, 'm' stands for the total of nodes in the resultant layer, while 'n' signifies the count of nodes in the initial layer.

(2) Identify the parameters of the RBF network that necessitate particle swarm optimization, and ascertain the architecture and magnitude of the particles

After determining the number of input layer, hidden layer, and input layer nodes, the RBF neural network parameters that need to be optimized using particle swarm optimization algorithm are the number of hidden layer center c_1, hidden layer width c_1, and connection weight w_1 from the hidden layer to the output layer. Should the hidden layer's core possess a dimensionality identical to that of the input layer, the count of hidden layers is determined by multiplying the dimension of the core by the quantity of cores. The hidden layer's width parameters tally with the number of its cores. The synapse weight is calculated by multiplying the number of hidden layer cores by the number of nodes in the output layer. This illustrates the number of undefined parameters that particles within the particle swarm optimization methodology are equipped with.

(3) Establish the optimization target within the particle swarm algorithm framework

Determine the output evaluation criteria of the RBF neural network model and use this evaluation criterion as the objective function of the particle swarm algorithm.

Use the particle swarm optimization (PSO) technique to ascertain the ideal parameters for the radial basis function (RBF) network

Establish the swarm size, the starting positions and velocities of the particles, and configure parameters including the inertia weight, cognitive and social coefficients, the number of iterations, and the upper limit for velocity. Determine the best initial individual position and the best overall swarm position. Adhere to the PSO iterative procedure to progressively refine the particle velocities and locations until the optimal solution is achieved.

Algorithm solving

Based on the data features discussed within this text, the proposed model incorporates 32 input neurons, 33 intermediate neurons, and a single output neuron.

The objective function is used to calculate the fitness of particles. Therefore, in this article, we determine the objective function of the particle swarm algorithm as follows:

$$MAE\left(y_i, y_i'\right) = \frac{1}{N}\sum_{i=1}^{N}\left|y_i - y_i'\right|$$

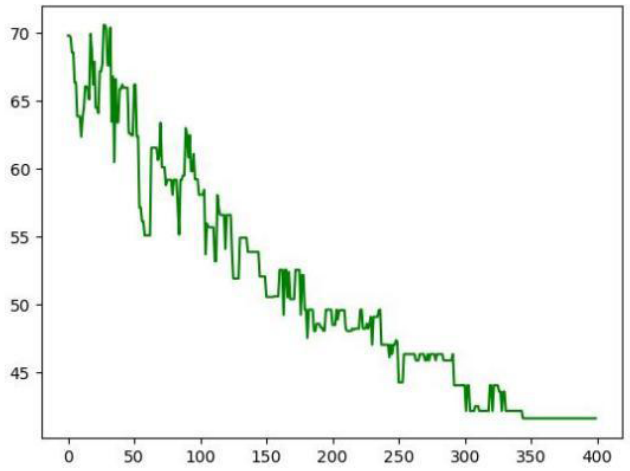
$$fitness = MAE\left(y_i, y_i'\right) + 1$$

Where: *fitness* represents fitness value; *MAE* represents the average absolute error; y'_i is the actual value of environmental pollution; y_i is the RBF neural network prediction value of environmental pollution; N is the total number of test samples.

Initialize the relevant parameters of the PSO algorithm: font size N=50; Iteration count T=500; R1 and r2 take a random number between 0 and 1; Learning factor c_1=c_2=2; In linear decreasing weight PSO, w_{max}=0.6, w_{min}=0.2.

After obtaining the optimal parameters of the RBF neural network using particle swarm optimization algorithm, these parameters are then assigned to the RBF neural network to obtain the model of the RBF neural network. Finally, we solved the problem by substituting the data, and the resulting solution is as follows,figure 7.

Figure 7: PSO Algorithm Iteration Results



In the end, we found through the solution results that the lower the fitness, the higher the accuracy of the algorithm, and reached the optimal parameters in the 242 nd generation.

In this study, the effects of melatonin on diabetic retinopathy were investigated at cellular level and global level by biochemical and molecular biology methods.

Further study on the role of diabetes mellitus and the risk factors affecting diabetic retinopathy, and further study on its mechanism of action, will provide theoretical basis for the development of new drugs for diabetic retinopathy protection and clinical trials, and provide a new way for the treatment of diabetic retinopathy.

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No

Conflict of Interests

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

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