1. Introduction

Nervous system plays an important role in the human body. It can coordinate voluntary and involuntary actions of other tissues and sub-systems. The nervous system can be divided into central nervous system (CNS) and peripheral nervous system (PNS) (Preston and Wilson, 2012). The CNS contains the neurons of the brain and spinal cord and it is the integrative and decision-making part of the nervous system. The PNS refers to parts of the nervous system outside the brain and spinal cord. It is a complicated, extensive network of nerves that collects sensory information and conveys it to the CNS for processing. Nerve tissue is mainly composed of neurons and supporting cells. The neuron can transmit action potential rapidly from one area of the body to the next. It can be divided into four zones as: cell body, dendrite, axon and nerve terminal. Depending on distribution in CNS and PNS the supporting cells have different types. The supporting cells of the PNS are Schwann cells that form myelin to wrap axon of the neuron.

In case the peripheral nerve is injured by trauma or neuropathy, the distal zone would be degenerated and the proximal zone may be regenerated to recover the peripheral nerve function. If the affected area is not cared properly it may become a neuroma that causes long-term nerve injury. Drug and physical therapy were commonly utilized to help the injured nerve to recover and regeneration. Diabetic neuropathy, carpal tunnel syndrome, and nerve trauma are common symptoms of nerve injuries in Taiwan and all over the world. The biomechanical properties of peripheral nerves are important factors of the repair and regeneration process of the nerve after injury (Sunderland, 1978). The goal of this paper is to review the researches done by members of Taiwanese Society of Biomechanics on the biomechanics of peripheral nerves in the past two decades. As a background, first, a brief introduction of the anatomy of peripheral nerve is given. Then experiment designs and mechanical models for testing the nerves are presented. The material properties ranged from linear elastic to nonlinear visco-elastic and scales ranged from organ level to tissue level are reviewed. Implications of these studies to clinical problems will be addressed and the challenges and future perspective on biomechanics of peripheral nerve are discussed.
2. Anatomy of Peripheral Nerves

The axons within the peripheral nerve are long extensions of their cell bodies located in the dorsal root ganglia, autonomic ganglia, or the ventral horn of the spinal cord or brain stem (Topp and Boyd, 2006). The axons are insulated from each other, bundled together, and protected by three main connective tissue layers, namely the endoneurium, the perineurium, and the epineurium (Fig. 1). The axon, myelin sheath, and endoneurial components are bundled by a perineurium layer to form a nerve fascicle. Several fascicles are held together by the epineurial connective tissue layer to form a peripheral nerve (Preston and Wilson, 2012). Within the endoneurium, nerve fibers are composed of myelinated and un-myelinated neuron axons. Each fascicle has motor, sensory, and autonomic nerve fibers or just one kind of them. Each myelinated axon is wrapped tightly by a Schwann cell for multiple turns to form a myelin sheath. At node of Ranvier two Schwann cells are separated. Unmyelinated axons are bundled together and enveloped by Schwann cell cytoplasm and plasma membrane. The endoneurium fills the inner space of each fascicle and it is consisted of fibroblasts, type I & II collagen fibrils, few mast cells and macrophages. The collagen fibrils are arranged longitudinally and with a diameter less than 50 nm. It forms an endoneurial tube that contains endoneurial fluid which provides inner pressure of the fascicle. If a fascicle is cut transversely, the inner components of the endoneurium are protruded to a mushroom shape. This pressure can make the fascicle stiffer (Lundborg, 2004; Spencer et al., 1975). The nerve fibers surrounded by the endoneurium have slightly undulating shape such that they can be stretched by a small initial tensile force on the nerve. The endoneurium can resist the outer tensile force but its stiffness is less than that of perineurium and the nerve fibers can be easily compressed and extended by external load (Sunderland, 1978).

![Fig 1. The ultra-structure and organization of a peripheral nerve.](image)

Perineurium is the thinnest but most dense layer of the three connective tissues. It protects the nerve fibers and maintains the inner pressure and stiffness of the fascicle. Fifteen layers of flat perineurial cells are tightly connected to each other within the perineurium. Type I & II collagen fibrils and elastic fibers are filled within the intersection of each layer. Most of these fibers are longitudinally and the rest are cross-over distributed to form dense network. The collagen fibril layers and perineurial cells provided the nerve enough strength against external load. Depending on the size of the fascicle the thickness of the perineurium ranged between of 1.3 to 100 μm (Sunderland and Bradley, 1961).

The epineurium is an areolar connective tissue to hold nerve fascicles together. For nerves having multiple fascicles, the epineurium is divided into epifascicular epineurium and interfascicular epineurium (Sunderland, 1978; Topp and Boyd, 2006). The epineurium is a loose structure to keep the nerve soft and serves as a buffer barrier to protect the inner fascicles against external load. The epineurium contained type I & III collagen fibrils, elastic fibers, mast cells, and adipose tissue. Most of the collagen fibers were longitudinally distributed and the rest were formed as randomly cross-over arrays. These fibrils were thicker than the other two connective tissues.

Similar to many organs, the peripheral nerves are highly vascularized tissues. Transmission of action potential and axonal transport are supported by nutrients supplied by capillary vessels. Intra-neural blood vessels are abundant in all layers of the nerve, forming a pattern of longitudinally oriented vessels (Lundborg, 2004). Based on location the blood vessels can be classified as extrinsic and intrinsic vessels. The extrinsic vessels support vascular plexus superficial and deep layers of the connective tissues. Intrinsic vessels are distributed inside the epineurium, perineurium, and endoneurium. Epineurial arterioles form an anastomotic network running longitudinally within the epifascicular...
epineurium and the interfascicular epineurium. Perforating arterioles intersect the perineurium at oblique angles. Peri-neurial arterioles slightly regulated intra-fascicular blood flow with poorly developed smooth muscles. Within the endoneurium the arterioles turn into large-diameter, longitudinally oriented capillaries. After that, venules return blood to the venous system. Generally, the inter-neural blood vessels including arterioles and venules could be defined as vasa nervorum (Moore and Dalley, 2006; Rohkamm, 2014).

The peripheral nerves are endured to various mechanical loads under normal physiological conditions imposed by human movements and postures, e.g., the nerve is subjected to tensile stress when joint motion caused elongation of the nerve bed. The carpal tunnel syndrome, a frequently encountered chronic peripheral neuropathy, and neuropathy caused by diabetes mellitus are due to long-term compression of the nerves (Main et al., 2011). When diabetic nerves are subjected to long-term compression, the blood vessels will be damaged followed by injury of the nerve fibers (Dyck et al., 1986; Dyck and Giannini, 1996).

3. Experiment and biomechanical model of peripheral nerves as a whole

According to the types of mechanical loads on the peripheral nerves in vivo, two kinds of mechanical tests have been designed, namely, the axial tensile test and transverse compression. The geometry of peripheral nerve is a long string with diameter 1.19 ± 0.10mm for rabbits, rats and 1.2-5mm for human. Therefore, customized testing devices have to be designed to perform in vitro or in vivo tests.

3.1 Axial quasi-static tensile testing. To study the repair of peripheral nerve a micro-tensile tester was first designed to measure in vitro mechanical properties of sciatic nerves of Wistar and Sprague-Dawley (SD) rats (Wong, 2005). The tester consists of a linear stage with a stroke of 100 mm and a ball screw with lead of 5 mm and a microprocessor controller. (Fig. 2) The stage is driven by a stepping motor that is controlled by the microprocessor. Two aluminum grips are utilized to clamp the nerve and one of the grips is fixed to a load cell with a capacity of 5 N and the resolution of force is 0.001 N. The other grip is fixed to the moving head of the linear stage. Two kinds of tests are conducted, namely the tensile test and the stress relaxation test. The results show that the ultimate stress, elastic modulus and failure strain are strain rate dependent. At a strain rate of 0.02 s⁻¹, the ultimate stress, elastic modulus and failure strain are 3.66 ± 1.20 MPa, 6.58 ±3.22 MPa and 0.91 ± 0.18, respectively and the corresponding values for 0.2 s⁻¹ are 4.72 ±1.21 MPa, 12.56 ± 4.11 MPa and 0.77 ± 0.27, respectively. The results confirm that the nerve is a viscoelastic material and microstructural analyses show the perineurium and epineurium were responsible for the tensile strength of rat sciatic nerve. The relaxation ratios are dependent on the initial strain rate and the holding strain at end of the tension phase. The stress relaxation ratio under a constant strain of 33% is greater than those under 50% and 66% at a low initial strain rate of 0.02 s⁻¹, however, no difference is found for initial strain rate of 0.2 s⁻¹. They suggested that the Kelvin model related the tensile stress \( \sigma \) and strain \( \varepsilon \), given by (Fung, 1993):

\[
\sigma + \tau_e \dot{\varepsilon} = E_e (\varepsilon + \tau_e \dot{\varepsilon})
\]

is well fitted with the relaxation behavior of the nerve. The parameters \( \tau_e \) and \( \dot{\varepsilon} \) are the relaxation time for constant strain and constant stress respectively and \( E_e \) is the relaxed elastic modulus. Using the same tester in a consequent study, the relationship between in vitro nerve-impulse conduction and tensile deformation of sciatic nerves of Long-Evan rat are studied (Chiou, 2006). They found that in the tensile test the compound nerve action potential amplitude drop depends on the strain level rather than the strain rate (Fig. 3). In the stress relaxation test, a higher holding strain would yield lower final compound nerve action potential amplitude. They suggest that the nerve-impulse conduction in rat sciatic nerve is dependent on the development of deformation-induced damage rather than on the stress level.

![Fig 2.](image-url) (a) The micro-tensile tester, (b) nerve and grips, by permission.

![Fig 3.](image-url) Normalized compound nerve action potentials vs. strain, by permission.
3.2 Axial Dynamic tensile testing. To study the sciatica resulted from spinal stenosis a custom-made clamp is integrated with a dynamic testing machine and in vivo test of an animal model of spinal stenosis is first performed (Huang, 2007). The biomechanical properties of rat sciatic nerve with cyclic movements of the hind limb in both normal and the model of spinal stenosis are compared. The custom-made system has a platform for holding the trunk of the rat and an adjustable linkage system that can clamp both thigh and shank of the rat and align joint center with the hip joint. The shank clamping link is rotated by a connecting rod with a joint actuated by the moving head of the dynamic testing machine (Fig. 4(a)). In particular, two barbs are pierced into the sciatic nerve and a differential variable reluctance transducer is utilized to measure displacements of the barbs and thus the strain and excursion can be obtained for different knee angles (Fig. 4(b)). In the animal model the extradural balloon compression technique is employed to induce spinal stenosis. Using 7 normal rats as the control and 8 rats with induced spinal stenosis as the experimental they find that the strain of sciatic nerve is increased significantly when the knee joint is extended from flexion 45 degrees to flexion 0 degree for both the normal and the spinal stenosis groups. On the contrary, the strain is decreased when the knee joint is flexed from flexion 45 degrees to flexion 90 degrees for all subjects and no significant group difference. As for the excursion, it is increased significantly in both groups when the knee is extended and decreased significantly when the knee joint is flexed. Besides significant group difference is found when the knee is extended. The results reveal that alteration of mechanical properties of the sciatic nerve following spinal stenosis and the excursion of the sciatic nerve is reduced while the nerve is stretched.

(a) ![Custom-made dynamic testing system](image1)
(b) ![Barbs and differential variable reluctance transducer](image2)

Fig 4. (a) Custom-made dynamic testing system for manipulating knee joint and measuring excursion and strain of sciatic nerve, (b) barbs and differential variable reluctance transducer, by permission.

In a consequent study, they utilize epidural balloon compression to induce acute cauda equina compression on Sprague-Dawley rats and measure excursions and strains of the sciatic nerve in response to the modified straight leg–raising test (Tai et al., 2015). They find that the excursion of sciatic nerve in the balloon group is lower than those of control and normal groups in both 90 degree flexion and full extension of the knee. The strain of sciatic nerve is increased significantly under epidural balloon compression. The cauda equina compression decreases the excursion and increases the strain of the sciatic nerve in response to a modified straight leg-raising test.

3.3 Transverse parallel compression testing. To design spiral cuff electrodes for motor neural prosthesis, in vitro transverse biomechanics of peripheral nerves was studied (Ju et al., 2004). A parallel compression test system was designed and built to compress the nerve segment transversely and to record images of the cross section of the nerve by using a camera mounted on a microscope (Fig. 5). The compression apparatus is consisted of a linear translation stage, a force transducer, a supporting platform and a movable plate. The stage has a precision of 0.5 μm for each step and the force transducer has a full capacity of 9.8 N and a resolution of 4.9 mN. A low-temperature light source is utilized to illuminate the sample and to prevent vaporization of tissue fluid in the nerve sample. Digitized images of the nerve cross sections are used to construct two-dimensional elastic models of the nerves. Software ANSYS is used to simulate the parallel compression tests and to estimate the apparent Young’s modulus of rabbit sciatic nerve from data of the applied force and the gap between the parallel plates. The results showed the mean Young’s modulus of rabbit sciatic nerves is 41.6±5.0 kPa. Comparing the finite element model simulation results and experimental data, it is suggested that the large fascicle is the main load-bearing component while the small fascicle and the loose connective tissues like the epineurium bear less load in the parallel compression process (Fig. 6).
3.4 Transverse quasi-static circular compression. The \textit{in vivo} loading condition of the nerve differs to that of \textit{in vitro} condition, therefore, a new \textit{in situ} circular compression testing system is developed (Ju et al., 2006). It can compress the nerve radially and measure indirectly the normal pressure or stress exerted on nerve surface. A laser Doppler flowmeter is employed to measure local nerve blood perfusion distal to the compressed site. The compression apparatus is consisted of a linear translation stage (precision 0.5 \(\mu\text{m}\)), a force transducer (capacity 1 N, resolution 4.9 mN), a supporting platform and a nerve compression part (Fig.7). The main component is a thin polyimide (PI) sheet (20 \(\mu\text{m}\) in thickness and 8 mm in width except 12 mm in width at center), with one end passing through a pre-cut slit at the center of the sheet. The central part of the sheet, thus, formed a tube wrapped around the nerve trunk. One end of the sheet was fixed to the supporting platform and the other end was fixed to the translation stage. The function of the supporting platform was to position the nerve compression part close to the exposed nerve \textit{in situ} without having to cut the nerve off. The laser Doppler flowmeter (Biopac, \url{http://www.biopac.com}) can measure blood perfusion unit (BPU) defined as the product of number of red blood cells per mm\(^3\) and mean flow velocity of red blood cells (mm/s). The experimental data, namely displacement of the linear stage, the tensile force pull by the stage, and BPU are digitized and stored in a personal computer at a sampling rate of 1000 Hz per channel. Assuming that the normal stress acting on nerve surface is uniformly distributed and using the work-energy principle, the radial normal stress (Eq.(5) in Ju et al., 2006) is given by (Fig. 8):

\[
\sigma_r = \frac{T}{(1 + 2\pi\mu)} rw
\]

where \(T\) is the tensile force pull by the PI sheet, \(r\) the radius of the nerve, \(w\) the width of PI sheet and \(\mu\) the frictional coefficient between the nerve and the PI sheet. The friction coefficient is measured using a freshly cut nerve segment and has a value of 0.35. The initial radius (\(r_0\)) of the sciatic nerve is estimated from the cross-sectional image of the nerve when it was cut down at end of the experiment. The radial strain is defined as:

\[
\varepsilon_r = \frac{r_0 - r}{2\pi r_0} = \frac{\Delta L}{2\pi r_0}
\]

where \(\Delta L\) is the displacement of the PI sheet from the initial position. Using the radial normal stress and radial strain the stress-strain curve of the sciatic nerve can be found to have an initial toe regime and a linear regime when the strain is greater than 0.2. The Young’s modulus is defined as the slope of the stress-strain curve of the linear regime. Results from quasi-static circular compression experiments on six rabbit sciatic nerves show the mean Young’s modulus of the sciatic nerves in the transverse direction is 66.9 \(\pm\) 8.0 kPa. The blood perfusion of the nerve starts to decrease at a mean pressure of 30.5 mmHg and reaches a stable lower level of 30\% of pre-compression value at 102.8 mmHg. Although the assumption of uniform normal stress during the circular compression may be too simplified, however, the developed methods provide a quantitative and consistent approach for elasticity of the sciatic nerve in the transverse direction. In a continued study (Chen et al., 2010a), the method is employed to study the effects of diabetes mellitus on the transverse elasticity and blood perfusion of sciatic nerve. Tests on six normal and six diabetic Wistar rats show that transverse apparent Young’s modulus of sciatic nerve of diabetic rats is nearly two times greater than that of normal rats. The pressure threshold for blood perfusion to decrease in diabetic rats is smaller than that of the normal rats (24.1 mmHg vs. 47.1 mmHg).
3.5 Transverse dynamic circular compression testing. In the abovementioned studies the sciatic nerve exhibits viscoelastic behaviors such as hysteresis and relaxation. In another study, the circular compression system is modified such that it can perform dynamic testing (Chen et al., 2010b). The translational stage of the circular compression system is replaced by a linear servo-motor (SGAM20-35, SIGMA) which has a velocity resolution of 0.5 µm/s. Using a personal computer to control the movement of the stage, dynamic tests including the ramp-and-hold (or compression-and-hold) and sinusoidal trials can be performed. The quasi-linear viscoelastic model (Fung, 1993) is employed to describe the biomechanical properties of the sciatic nerves of rats. In particular, the distribution of normal stress on the surface of nerve is re-derived and the correct average normal stress is given by:

\[
\sigma_r = \frac{1}{2 \pi \mu r_w} \left( T - \frac{T}{e^{\tau r}} \right) \tag{4}
\]

The quasi-linear viscoelastic model of the nerve is given by:

\[
\vec{\sigma}_r(\varepsilon_r, t) = \int_0^t G(t-\tau) \cdot \frac{\partial \vec{\sigma}_r^{(0)}(\varepsilon_r)}{\partial \varepsilon_r} \frac{\partial \varepsilon_r}{\partial \tau} d\tau
\]

where

\[
\vec{\sigma}_r^{(0)}(\varepsilon_r) = A \left[ \varepsilon_r(t) \right]^B
\]

\[
G(t) = \frac{1 + C \cdot \left[ E_r(t/\tau_2) - E_r(t/\tau_1) \right]}{1 + C \cdot \ln(\tau_2/\tau_1)}, \quad E_r(z) = \int_t^{z} e^{-\tau} d\tau \quad (|\arg z| < \pi)
\]

The model parameters, namely A, B, C, \(\tau_1\) and \(\tau_2\) are determined by minimizing the squared errors between the model predicted (Eq.5) and the measured (Eq.4) normal stresses. To save the computational time, the convolutional integral Eq.(5) is transformed to frequency domain and all the parameters can be obtained together instead of solving two sequential optimization problems (Abramowitch & Woo, 2004). Six normal and five diabetic neuropathic Wistar rats were tested to study effect of acute diabetes mellitus on the viscoelasticity of the nerve. We find that the model derived from the high strain rate (0.1s\(^{-1}\)) data could predict the responses of lower strain rates (0.05 and 0.01 s\(^{-1}\)) satisfactorily. The computation time is cut down 49.0% by using the technique without increasing the root-mean-square error. The percentage of stress relaxation of the diabetic and normal rats, calculated from the experimental data, is not significantly different. The diabetic nerves have smaller parameter C than that of the normal nerves (0.27±0.06 vs. 0.20±0.02, p < 0.05) indicates that they have smaller amplitude of viscous response or stress relaxation. The diabetic nerves have a larger parameter \(\tau_2\) implies that they need a longer relaxation period to reach equilibrium. An efficient algorithm for estimating parameters of quasi-linear viscoelastic model is developed and applied to the transverse biomechanics of sciatic nerves.

4. Experiments design and biomechanical models of peripheral nerves at ultra-structure level.

In above-mentioned studies, the nerve is postulated as a homogenous material, however, from histological point view it is heterogeneous and variations of mechanical properties among its three ultra-structures, namely epineurium, perineurium and endoneurium have to be considered. With the advances of imaging systems such as the optical coherence tomography (OCT), it becomes possible to explore the mechanical behaviors of the ultra-structures of the nerves. In addition, using the Doppler optical coherence tomography the blood flow within vasa nervorum can be visualized and used to locate lumen of the blood vessels. Integrated the OCT images with transverse images of the micro-slices of the nerve, a geometric model consisted of the ultra-structures and blood vessels can be established and utilized in finite element analyses.

4.1 In vitro dynamic parallel compression testing. To build a two-dimensional structural model of the sciatic nerve, a
parallel compression device that can be mounted on an OCT is designed (Chen, 2013, Chang et al., 2015). The testing system can perform compress-and-hold of the nerve and acquire structural images concurrently. Figure 9 shows schematic diagram of the compression apparatus and OCT. The apparatus consists of a specimen fixture, a unit-axial force transducer, a DC servomotor and two glass plates. The upper glass plate is mounted on the platform and the bottom glass plate is placed against the force transducer which is moved up and down by the servo motor. The OCT can acquire the cross-sectional images of the nerve with a range of 10 mm x 10 mm x 3 mm and longitudinal resolution of 9 μm and scanning rate of 24 frames per second. The structural image of the nerve at zero-stress state is converted into a grey-scale image then outer boundaries of epineurium and perineurium are marked manually by using the image processing toolbox of MATLAB. The coordinates of boundary points of the nerve images are imported into finite element software ABAQUS v.6.11-1. The thickness of the perineurium can not be identified from OCT image and is assumed to be 3% of diameter of the fascicle (Grinberg et al., 2008). Figure 10 shows the OCT image and geometric model of the ultra-structure of a sample. All the ultra-structures of nerve are modeled as isotropic, homogeneous and incompressible and hyper-viscoelastic material.

\[
W_i(t) = \frac{2}{\alpha_i^2} \int_0^t G(t - \tau) \frac{d}{d\tau} \left( \lambda_i^{\alpha_i^n} + \lambda_j^{\alpha_j^n} + \lambda_k^{\alpha_k^n} - 3 \right) d\tau, \quad i = 1, 2, 3
\]

where subscript \(i\) is 1 for epineurium, 2 for perineurium and 3 for endoneurium and \(\lambda_i\) the principal stretch ratio. For simplification, all ultra-structures are assumed to have same reduced relaxation function (second-order Prony series, \(t\) is time). \(\alpha_i\) is the material parameters and \(G_{\alpha_i}\) is the instantaneous shear modulus, \(g_{ij}^p\) is the Prony constant and \(\tau_i\) is the retardation time constant. An inverse finite element analysis problem is formulated as the minimization of the squared errors between the measured force and predicted force obtained from finite-element simulation. The simulated annealing method (Kirkpatrick et al., 1983) in MATLAB optimization toolbox is employed to solve the problem. Figure 11 shows a typical force history compared with optimized FE results and deformed nerve ultra-structure and distribution of normal stress of same nerve. The root mean squared error of force history is 0.0091 N and high level of normal stress appears on the right fascicle and the left and right-outter boundaries of the epineurium are subject to tensile stress. The difference of the contours of the fascicles obtained from OCT and FE simulation may be due to the damage of the interface between perineurium and the epineurium and escaping of tissue fluids during the compression phase.
4.2 **In situ dynamic circular compression testing.** To study the effects of diabetes mellitus on the cause of ischemia of vasa nervora, the circular compression testing system is integrated with the optical coherence tomography microscope (Tang, 2016). In particular, the Doppler OCT is employed to obtain the cross-sectional area of vasa nervora during *in situ* circular compression of the sciatic nerve of diabetic rats. A statistical method is utilized to improve the quality of images of blood flow distribution and for better estimation of the lumen area of main vasa nervorum. Figure 12(a) shows a Doppler OCT image of nerve tissue where a blood flow region with colors shifted to orange can be observed. By mapping the RGB values of each pixel to a two-dimensional color space (CIE 1931 color space, defined by International Commission on Illumination), the blood flow region can be registered from the coordinate difference or color shift in the color space. To explore the effects of circular compression on the vasa nervora of diabetic nerves, five time periods of image series as following were analyzed: (i) 3 minutes before compression test (~2700 images), (ii) maximum compression strain (10 s ~ 20 s, 150 images), (iii) middle of holding phase (310 s ~ 320 s, 150 images), (iv) end of holding phase (610 s ~ 620 s, 150 images), (v) 3 minutes after decompression (nerve released, 2700 images). In each period of time, a series of Doppler OCT images are acquired and the number of color shifts is counted. The histogram of numbers of color shift for all pixels of the image can be found and a threshold of 5% of maximum count number among all the pixels was used to find the contour of the lumen of vasa nervorum (Fig.12(b)). The distortion of OCT images caused by the refractive indices of materials along the path of coherent laser light is corrected using refractive indices of saline water, epineurium and red blood cells within the vasa nervorum. The geometric model of the nerve tissue and vasa nervora is constructed based on the corrected OCT image and the tissue slices. Similar to above study, a finite element model is built using software ABAQUS v.6.11-1 and same material properties (Eq. 6) and the lumen of blood vessel is postulated as isotropic nonlinear elastic material. Loading and boundary conditions in FEM analysis are similar to those in the compress-and-hold experiment to simulate *in situ* circular compression. Figure 13 shows the stress distribution and deformation of a diabetic nerve obtained from FEM analyses. The diabetic nerves are more viscous and their vasa nervora are more vulnerable to circular compression. The blood vessels resided in the saddle regions of epineurium have lesser tendency to collapse under the circular compression.
In Table 1 list the mean values of the material constants of the models reported in the reviewed works. For the elastic model, the axial elastic modulus is greater than that of the transverse elastic modulus, indicating the nerve is anisotropic and prone to injury due to transverse load such as compression in carpal tunnel (Wong, 2005, Ju, 2004, 2006). For either linear or nonlinear elastic models the modulus of diabetic nerve is greater than that of the normal nerve, indicating hardening of nerve is related to diabetes mellitus (Chen, 2010a, Chen 2010b). For the quasi-linear viscoelasticity model, the value of parameter C for the diabetic nerve is smaller than that of the normal nerve, revealing the diabetic nerve is less viscous than the normal nerve. Similar results can be found for the testing of fascicles (Chang, 2016). At the tissue level, the stiffness of the ultra-structures in descending order is: perineurium, endoneurium and epineurium, suggesting the perineurium is the main bearing structure for transverse compression. Similarly, the stiffness of these ultra-structures for the diabetic nerve is greater than that of the normal nerve and the diabetes mellitus affected ultra-structures are less viscous than the normal ones (Chen, 2012, Tang, 2016). The Doppler OCT results reveal the collapse of blood vessels within the epineurium of the diabetic nerve, revealing alteration of mechanical properties of these blood vessels.

5. Implications of biomechanics of peripheral nerves to clinical problems and biomedical engineering

Although the main function of peripheral nerve is conduction of afferent and efferent signals in the nervous system. The reviewed studies show that biomechanical factors, e.g. blood perfusion, viscoelasticity of nerve tissues, and elasticity of vasa nervorum are different among the healthy and the pathological nerves and may affect the normal functions of peripheral nerves. The complexity of models depends on the applications of the model. For the design of nerve cuff electrodes, safety of nerve repair surgery and cauda equine compression study, one-dimensional model for longitudinal tension or transverse compression may be sufficient. However, for studying the neuropathy and carpal tunnel syndrome a structural model is necessary to analyze the stress distribution within the ultra-structures of the nerve and viscoelastic behaviors of tissues has to be considered due to the physiological load on nerves is often dynamic rather than quasi-static. With these studies, the allowable normal stress acted on nerve by spiral cuff electrode, the difference between viscoelasticity of diabetic and healthy nerves for rats at organ and tissue levels, mechanism of pain induced by cauda equine compression are found. In particular, the hardening of ultra-structures and the alteration of mechanical behavior of the blood vessels within the peripheral nerves may be the biomechanical factors of the neuropathy due to diabetes mellitus.

6. Future perspectives

The major function of the peripheral nerve comes from the nerve fibers resided within the fascicles or the endoneurium. To explore the mechanism of nerve regeneration after injury further study on the biomechanics of myelinated or unmyelinated nerve fibers is necessary. The challenge will be the design of in vitro and in vivo testing methods. Although biomechanics of PC-12 cells and their co-cultured with Schwann cells have been studied by nano-indentation and atomic-force microscopy (Huang et al., 2011, Hsu, 2013). How to do in vivo testing remains a challenging problem. The other aspect is mechanical behaviors of the interface between the three ultra-structures of the nerve, especially the interface between the epineurium and the perineurium. The strength of the interface is quite low such that the fascicles can be peeled off very easily during dissection of the nerve. The strength of the interface may affect the over-all mechanical property of the nerve especially in finite element analyses. In the inverse finite element analyses of nerve tissues, an optimization problem is formulated and often multiple solutions are obtained and methods for choosing a reliable solution have to be developed. Objective functions which include more experimental data such as the geometry of deformed fascicle may be considered. The other approach is to isolate the fascicle and test it using miniaturized testing system (Chang et al., 2016). The integration of biomechanics at cellular level to that of the organ and tissue levels remains a challenge problem.

The applications of the reviewed works focus on the repair of peripheral nerves, the sciatica resulted from spinal stenosis and the chronic effects of implants and metabolic diseases (such as diabetes mellitus) on peripheral nerves. Besides these, the influence of peripheral nerve injury on CNS and biomechanics of peripheral nerves subjected to high strain rate loading in some trauma cases are also important problems. Although in the circular compression tests, radial strain rate as high as 0.1/s was applied and the quasi-linear viscoelasticity model can predict responses for lower strain rates (Chen 2010a).

In conclusion, the studies of biomechanics of peripheral nerves in the past two decades in Taiwan are reviewed and future aspects of the problem are discussed.
Table 1 Summary of experimental methods and biomechanical models for peripheral nerves

<table>
<thead>
<tr>
<th>Authors</th>
<th>Testing method</th>
<th>model</th>
<th>Mechanical properties</th>
<th>year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ju, M.-S. et al.</td>
<td>in vitro parallel compression</td>
<td>2D isotropic linear elastic</td>
<td>Elastic modulus 41.6 KPa</td>
<td>2004</td>
</tr>
<tr>
<td>Wong, Y.-C.</td>
<td>in vitro tensile</td>
<td>1D isotropic linear elastic</td>
<td>Elastic modulus 6.58 MPa (strain rate 0.02s^{-1}) and 12.56MPa (strain rate 0.2s^{-1})</td>
<td>2005</td>
</tr>
<tr>
<td>Ju, M.-S., et al.</td>
<td>in situ circular compression</td>
<td>1D isotropic linear elastic</td>
<td>Elastic modulus 66.98 KPa</td>
<td>2006</td>
</tr>
<tr>
<td>Huang, Y.-B.</td>
<td>in vivo, tensile</td>
<td>1D isotropic linear elastic</td>
<td>not reported</td>
<td>2007</td>
</tr>
<tr>
<td>Chen, R.-J., et al.</td>
<td>in situ transverse, blood perfusion</td>
<td>1D isotropic linear elastic</td>
<td>Elastic modulus for diabetic nerve 210.7 KPa, for normal nerve 116.3 KPa</td>
<td>2010</td>
</tr>
<tr>
<td>Chen, R.-J., et al.</td>
<td>in situ circular compression</td>
<td>1D isotropic quasi-linear viscoelastic</td>
<td>A: 973KPa vs. 1027 KPa*  B: 3.60 vs. 4.76*  C: 0.26 vs. 0.20*  t_1: 4.62 ms vs 2.86 ms*  t_1: 199 s vs 519 s*</td>
<td>2010</td>
</tr>
<tr>
<td>Chen, Y.-H.</td>
<td>in vitro parallel compression, OCT</td>
<td>2D hyper-viscoelastic, FEM, Ogden model, Eq.(6)</td>
<td>G_{01}=22 KPa, G_{02}=89 KPa, G_{03}=55 KPa, \alpha_1=8.396, \alpha_2=8.942, \alpha_3=6.949  g_1^<em>=0.232, g_2^</em>=0.305, \tau_1=29.09, \tau_2=50.47</td>
<td>2012</td>
</tr>
<tr>
<td>Tai, T.-W., et al.</td>
<td>in vivo, tensile</td>
<td>1D isotropic linear elastic</td>
<td>not reported</td>
<td>2015</td>
</tr>
<tr>
<td>Chang, C.-T., et al.</td>
<td>in vitro parallel compression, AFM</td>
<td>1D isotropic quasi-linear viscoelastic for fascicle</td>
<td>A: 0.423N/m vs. 0.818 N/m\textsuperscript{+}  B: 1.323 vs.1.303\textsuperscript{+}  C: 4.387 vs. 0.301\textsuperscript{+}  t_1: 0.009 s vs 0.002 s\textsuperscript{+}  t_2: 11070.3 s vs 11787.6 s\textsuperscript{+}</td>
<td>2016</td>
</tr>
<tr>
<td>Tang, C.-W.</td>
<td>in situ circular compression, Doppler OCT</td>
<td>2D hyper-viscoelastic, FEM, Ogden model, Eq.(6)</td>
<td>G_{01}=22 KPa vs. 37.89 KPa**  G_{02}=89 KPa vs. 164.65 Kpa **  G_{03}=55 KPa vs. 92KPa**  G_i=700KPa, \alpha=1.1 (normal &amp; diabetic) collapse of vasa nervorum in epineurium of diabetic nerve</td>
<td>2016</td>
</tr>
</tbody>
</table>

*healthy nerve vs. diabetic nerve, definition of parameters referred to Eq.(5), ** healthy nerve vs. diabetic nerve Eq.(6)  
\textsuperscript{+}healthy nerve vs. diabetic nerve, similar to Eq.(5) except that stress is replaced by force and strain by displacement  
\textsuperscript{e}F_{c}\textsuperscript{e}=A_{c}\textsuperscript{e} \delta_{c}\textsuperscript{e}  

Acknowledgements:

References


Chiu, S.-W., The Relationship Between Nerve-Impulse Conduction and Tensile Deformation in Rat Sciatic Nerve, M.S. Thesis (2006), Dept. of Mechanical Engineering, National Central University, Chung-Li, Taiwan.


Preston, P. P. and Wilson, T. E., Physiology (2012), Lippincott Williams & Wilkins, Baltimore/Philadelphia.


Tang, C.-W., Effects of Diabetes Mellitus on Mechanical Behavior of Peripheral Nerve Tissues and Vasa Nervora under...
