

The black box of a mysterious disorder

Fighting pain with mechanical perturbation systems

'It turned out that the medical profession did not fully understand the dynamics of body reflexes.'



Red and swollen limbs that feel hot or cold, a numb feeling, lack of mobility, and worst of all, pain. These are symptoms of post-traumatic dystrophy (PD).

Researchers from various disciplines are working together in the TREND research consortium to open the 'black box' of this mysterious disorder. Mechanical engineers at TU Delft are using mechanical perturbation systems to determine the neurological causes of the disorder.

They have developed three test rigs that can be used to find out what is wrong with the central nervous system of individual PD patients. In collaboration with American neurologist, David Bashor, the Delft researchers have been the first to link a Biological Neural Network model with 2300 neurons to a musculoskeletal model. They managed to simulate the motor symptoms of the PD patients by blocking a specific connection between two types of neurons in the model. Together with medical researchers from five teaching hospitals they are now looking for the underlying cause of the disorder that will explain other symptoms such as pain, skin ailments, and gastro-intestinal complaints.



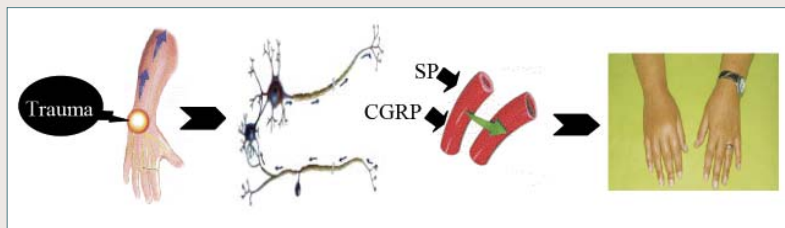
At the Leiden University Medical Centre a patient suffering from Post-Traumatic Dystrophy receives intravenous medication to relieve the pain and the effects of dystonia.

MAARTEN VAN DER SANDEN

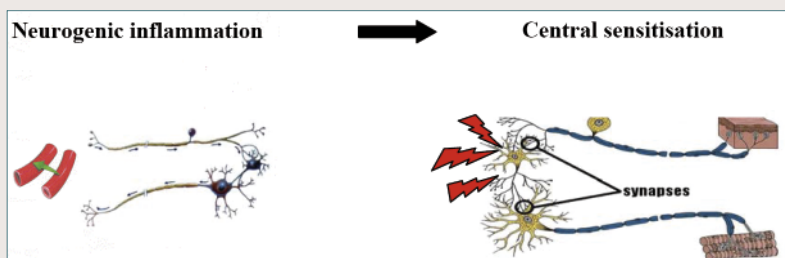
(PHOTOGRAPH: AVC LUMC-LEIDEN)



Post-Traumatic Dystrophy can cause dystonia, a condition in which the patient's hands and feet assume a typical claw-like configuration which can lead to severe immobility.



One of the hypotheses regarding the cause of Post-Traumatic Dystrophy is that the trauma results in a defensive action by certain nerve fibres, which will then secrete neuropeptides (natural drugs produced by the body) in the skin. These neuropeptides cause inflammation, resulting in oedema and skin discoloration.



In addition to inflammation of the skin, Post-Traumatic Dystrophy can also cause changes in the central nervous system, called central sensitisation. The violent pain and motor defects are probably caused by this effect.



These hands show different levels of dystonia in PD patients. The disorder often affects several extremities, both left and right, and arms and legs.



Dystonia and oedema in a patient's leg.

People suffering from post-traumatic dystrophy are often in severe pain, with their hands and feet particularly affected.

"This form of dystrophy is the result of an abnormal, post-traumatic response of the body to a minor injury, e.g. a sprained ankle or a small cut," says Dr. Frank Huygen, anaesthesiologist and head of the Pain Centre at the Erasmus Medical Centre, Rotterdam. "The excessive body response causes the tissue of the hand or foot to become damaged, resulting in pain, numbness, discolouring, and swelling."

According to Huygen the constant pain signal from the limb to the spinal cord can cause the latter to become hyper sensitised, so the spinal cord itself will start to transmit the pain signal, regardless of the signal coming from the hand. The changes in the interneurons of the spinal cord can presumably also cause dystrophy in other parts of the body.

In addition to pain, a number of other motor problems play a role in PD: a feeling of weakness in the hand and arm, or clenching of the hand into a typical claw state called dystonia. Uncontrollable trembling and stretching movements are also possible.

According to the Dutch Association of Post-traumatic Dystrophy Patients, the disorder affects 8,000 people every year, and the number of chronic PD patients is at least 20,000. Most patients develop the disorder as the result of some kind of injury.

Literature records at least 72 different disorders that come with the same symptoms. This is the reason that it is known as a syndrome. The complex of symptoms has for the last ten years been known as the Complex Regional Pain Syndrome (CRPS).

Cytokines "The disorder is highly incapacitating", says Huygen, "and there is still no definite treatment, simply because PD is not fully understood. It is high time to start looking at this syndrome in detail."

In 2004 Huygen was awarded his doctorate at the Erasmus Medical Centre for his research on the role of cytokines (messenger chemicals inside the body) and the inflammation of hands and feet as a result of PD. He demonstrated that patients suffering from PD produced too much of the messenger chemical interleukine-6 (IL-6) and too much Tumor Necrosis Factor (TNF α), when these substances were no longer required. Normally, interleukines are chemicals produced by the body to either suppress or stimulate inflammation. In the case of Complex Regional Pain Syndrome, however, the production system has run out of control so it actually causes an inflammation.

Huygen: "We have been able to demonstrate the presence of excess IL-6 and TNF α in fluid extracted from blisters we produced on the skin of patients near the inflammation."

Huygen created the blisters by applying a vacuum instrument to the skin. "Knowing this, we went on to look for treatment options using anti-TNF α ", Huygen continues. "This substance, which also helps to fight rheumatoid diseases, appears to work, since the inflammations showed clear signs of subsiding. We are currently engaged in a large clinical trial to see if we can help these patients."

Multidisciplinary Although the research by Huygen and others is an important step towards finding a treatment for patients, much more knowledge is required for the prevention, diagnosis and treatment of CRPS. That is where the research activities of the multidisciplinary Dutch team come in. The team unites researchers from Delft University of Technology, Leiden University Medical Centre, Erasmus Medical Centre, Amsterdam VU Medical Centre, Maastricht Academic Hospital, University of Utrecht and companies such as Noldus IT and FCS Control Systems. The name of the new research consortium is TREND (Trauma Related Neuronal Dysfunction).

At TREND, each member approaches the problem from his own discipline. At Leiden University for example, researchers are looking for the genes that are involved with the disorder. The researchers at Delft University are developing new measurement instruments to establish quantitative records of patients' symptoms. And, as mentioned above, the biochemical mechanisms of the disorder are being studied at Erasmus Medical Centre.

The TREND research effort at Delft University, headed by Professor Frans van der Helm, focuses on the development of diagnostic instruments. In addition, the research results provide insight into the way the disorder develops and how

to fight it. The research emphasis is on dystonia, a condition in which the hand or arm becomes distorted by a state of spasm. Knowledge of mechanical control systems turns out to be extremely useful in helping to understand dystonia. For some time now, Van der Helm and his group have been researching the human neuromuscular system. They have for example developed the Delft Shoulder and Elbow Model, which was used to demonstrate that ever since 1900 the medical profession has had a completely incorrect idea about the way the shoulder mechanism works (see Delft Outlook 91.3).

Van der Helm: "The shoulder, i.e. the complex of upper arm, shoulder blade, and clavicle, can make complex movements using a large number of different muscles. Due to its high level of complexity, it has taken us until recently to gain a modicum of insight into the way the shoulder joint works. This newly gained knowledge now comes in very useful for improving the diagnosis and treatment of shoulder complaints, and research into such fields as wheelchair motion and the design of shoulder prostheses."

Reflexes Van der Helm and his researchers, Erwin de Vlugt and Alfred Schouten (both of whom were awarded their doctorates last year), are interested in particular in muscle reflexes. De Vlugt and Schouten are now working on post-doctoral assignments within TREND to investigate reflexes in connection with PD.

Reflex pathways in the human body run through the spinal cord and are beyond conscious control of the brain. A familiar example of a reflex is the way we pull back a hand when we burn a finger. The signal of the excess temperature is received through the finger, and motor neurons in the spinal cord immediately activate the arm muscles to pull back the hand in order to prevent further injury. Reflex pathways form an important part of the human neuromuscular system. The muscles themselves contain proprioceptors, sensors that transmit information to the central nervous system about the position of our muscles, but also about a muscle's contraction speed and contraction force. The system enables us to move with more accuracy and, for example, hold an electric drill in position in spite of the disturbing forces coming from the rotating drill. If you were to try to correct the drill using conscious control from the brain, you would always react too late. Due to the fact that the body uses unconscious, fast reflexes, we manage to compensate for such disturbing forces.

"All these factors together make for a highly interesting control system", Van der Helm says. "In the field of mechanical engineering, one would never develop a robot without some means of feedback using sensors and a control system. Most robots completely rely on "reflex pathways" to generate preprogrammed motions and to stabilize the motions when they are disturbed by outside factors. Therefore, the technical model of the robot can ultimately serve as a test case for the human situation."

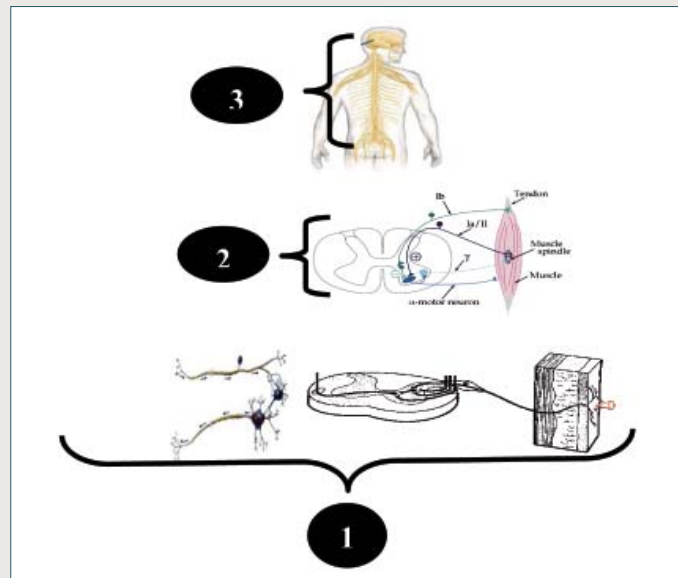
Damping Apart from the way the reflex pathways work, much of the outside disturbance acting on the human hand will be compensated for by the rigidity of bone and tissue.

Van der Helm: "These can be considered to be the intrinsic values, the dynamic mechanical properties, of the hand and arm. They include such parameters as the mass of the arm, the damping caused by the tissue, and the stiffness and viscosity of the muscles. The way in which the reflexes are modulated depends to a great extent on this set of parameters."

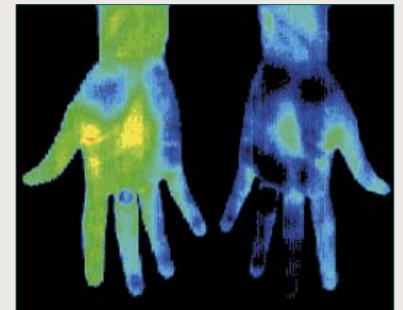
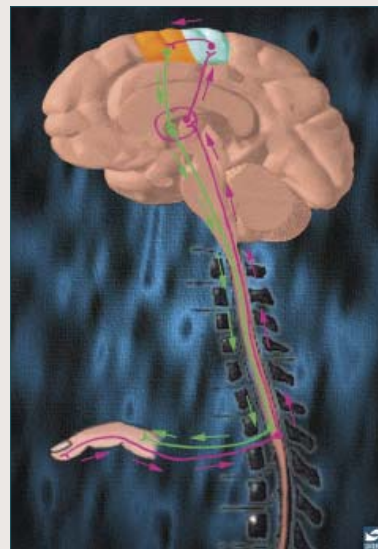
In a scientific article for the *Journal of Neuroscience Methods*, Van der Helm also demonstrates that factors such as frequency of the disturbance play a role in the way in which reflexes are adapted to neutralise the outside effects as much as possible. In the article the Delft researchers compared disturbances with a relatively high frequency content and disturbances with a relatively low frequency content.

So for reflex movements, the researchers are looking at three different factors: the nature of the disrupting effect on the arm (e.g. the frequency), the intrinsic properties (such as mass, rigidity, and muscle damping) of the hand and the arm, and the way the reflex pathways work.

Van der Helm: "In other words, this means that we are looking at controlling and measuring movement at several levels. In itself, this is nothing new in control systems, but it will be if we use the knowledge to find out how dystonia is caused as a result of PD. Which neurons, and consequently, which muscles are controlled and how does it result in the claw-like distortion of a hand?"



The true cause of PD is still unclear, and there may be several. Symptoms in PD patients point to the involvement of both peripheral and central mechanisms. Local inflammation responses are caused by skin nerves going out of control (1). Motor disorders in the reflex pathways point to the involvement of the spinal cord (2). Brain activity also shows discrepancies between patients and healthy test subjects (3).



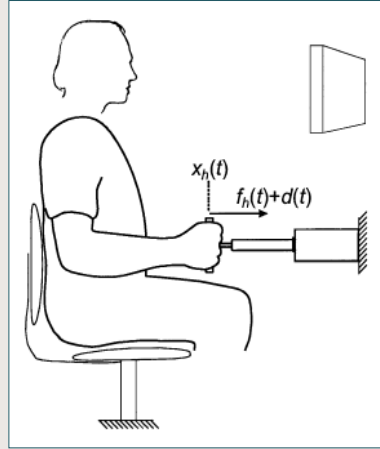
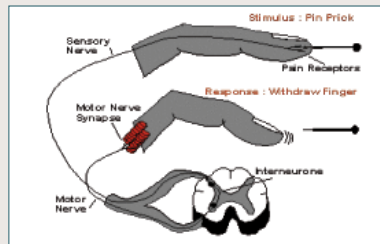
In PD patients, the temperature control system of the central nervous system is also affected. At the Erasmus Medical Centre in Rotterdam the skin temperature (a symptom) is being objectively measured using infrared cameras.

Patients suffering from PD probably have a genetic disposition that makes them susceptible to the disease, as a result of which a minor trauma, for example a small cut to the hand, can trigger a chain reaction of disordered peripheral and central mechanisms. One of typical symptoms is the violent pain resulting from hypersensitive responses of the spinal cord, called central sensitisation.

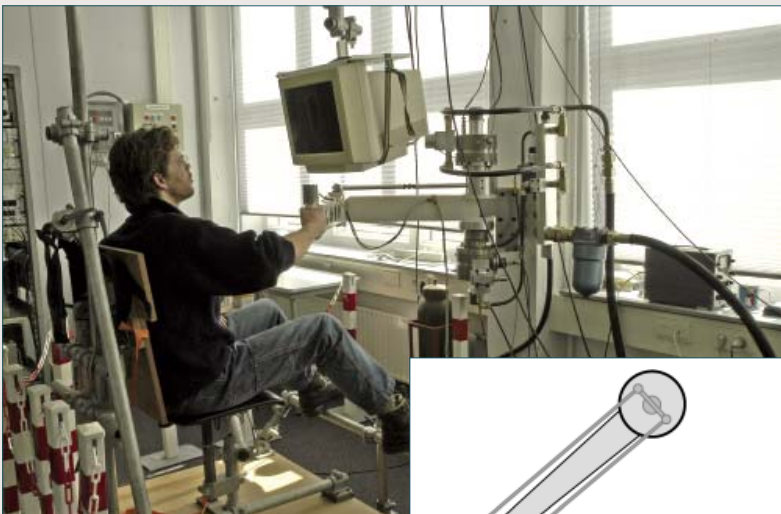


At the Erasmus Medical Centre blisters are produced on the skin of PD patients using a vacuum instrument. Fluid extracted from the blisters is screened at the Utrecht Medical Centre for hundreds of different proteins that are potential biomarkers which could be used to unequivocally determine the presence of PD.

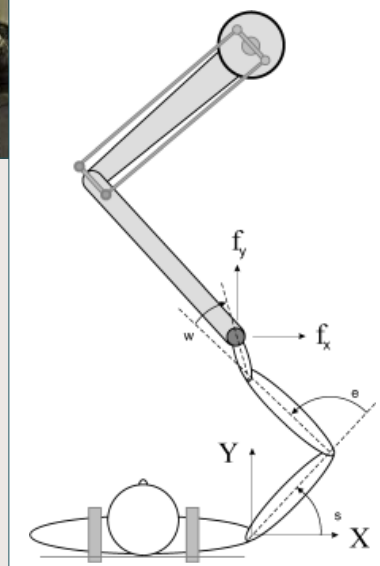
Motor symptoms such as dystonia (a kind of muscle spasm) are caused by defects in the reflex pathways of the spinal cord. By measuring the entire chain from sensors (muscle spindles), controlling mechanism (central nervous system), and actuators (muscles), researchers from Delft University can map the disorders of the neurons in the spinal cord.



Researchers at the Neuromuscular Lab of TU Delft have developed very powerful hydraulic manipulators that enable them to apply high-frequency force disturbances, so they can calculate the strength of the position, speed, and force feedback pathways. This is currently the only lab in the world with this capability. The single freedom manipulator uses a piston rod that moves a handle to and fro. A PD patient is asked to keep the handle in one place while disturbing forces are applied to it. This is a very natural task ("keep your hand in one place"). The arm stiffens because the muscles contract (cocontraction) and because of natural reflexes. Reflex pathways are closed feedback loops that normally serve to counteract disturbances. The only mathematical way to reliably calculate variables within the feedback loop is by applying disturbances of a known pattern into the closed loop and observe the variables inside the closed loop to vary with the disturbance pattern. The force and the position of the hand and the electrical activity of the muscles are measured to determine the feedback gains.



Using the new 2 degree-of-freedom manipulator, the handle can be moved within a horizontal plane. This device can be used to simultaneously measure the muscles around the shoulder, elbow, and wrist. Using an advanced model, the reflex strength can be calculated for each muscle group. This machine can be used to investigate the complex coordination between joints as well as the strength of reflexes during motion.



Light Van der Helm and his researchers are trying to gain insight into this complex system of factors by means of a robot manipulator which imposes force perturbations on the subjects (PD patients and healthy controls), results of which are recorded in details. The setup comprises a hydraulic actuator attached to a handle. The test subject is seated and grabs the handle. The lower arm is in a horizontal line with the direction in which the piston and handle move. The force exerted by the test subject on the handle is measured, and a high-speed control circuit then calculates the corresponding position. Next, a randomly varying pressure (disruption) results in disturbing forces that are felt by the test subject. It's rather like wind acting on an umbrella one is trying to hold up to the rain.

The test subjects are asked to keep the handle as much as possible in the starting position. They will contract all their muscles to make the arm as rigid as possible (co-contraction), but they will also unconsciously start to use their reflexes to counteract the handle's movements. The force exerted by the test subjects and the position of the handle are continuously recorded, as is the disturbing force acting on the handle.

The entire system can be modelled as a mass-spring system with damping in which the reflexes act rather like delayed-action springs and dampers, the nerves. The model can be analysed using the principles of mechanical control systems. The measuring process is complemented by a series of electromyographs of the test subjects as they try to hold the moving handle in one place. The EMGs are used to map the electrical muscle activity under various loads.

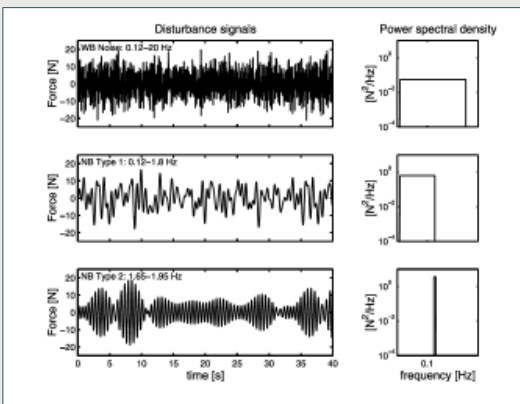
By combining all the data from various disturbance frequencies and analysing the results using methods for control systems, Van der Helm can separate the effects of the various reflex pathways and those of the intrinsic properties of the arm. It also helps to determine the effect of the reflexive feedback. The Delft group of mechanical engineers is the first in the world to be able to measure quantitative data of both the position, speed, and force feedback pathways of the arm reflex. Since the strength of the reflexes is controlled by the interneurons in the central nervous system, which act as switching stations, the results also provide insight into the way the central nervous system works. In close collaboration with the Neurology and Rehabilitation departments of the Leiden University Medical Centre, similar research is being done with patients with neurological disorders caused by a cerebral haemorrhage (stroke) or Parkinson's disease for instance.

ARMANDA Having gained the necessary knowledge from his experimental research, Van der Helm will be able to determine which muscle contractions are stimulated and suppressed by which reflex pathways. For example, measurements of the force disturbance experiments have shown that dystonia as a result of PD coincides with excessive control action in the reflex pathway of the muscle. The reflex strength determines the extent of muscle activation as a result of the disturbance, e.g. sudden stretch of a muscle. High reflex strength leads to excessive responses, whereas a low reflex strength causes hardly any muscle activation at all. The reflex strength is determined by signals from the brain that modulate the sensitivity of interneurons in the spinal cord through inhibition of the interneurons. If these signals from the brain are lost, the interneurons become over sensitised, resulting in exaggerated reflexes that cause the muscle to become convulsed and stop moving at all.

Recently, Van der Helm's group have started using a new, expanded and improved measuring machine (ARMANDA), designed in collaboration with colleagues from the Systems and Control Group. The new machine enables the group to research the body's reflex pathways in even greater detail. For example, ARMANDA can be used to simultaneously simulate and analyse more complex movements of the shoulder, elbow, and wrist. In his thesis, Erwin de Vlugt demonstrated that advanced mathematical methods can be used to distinguish between the reflexes of the monoarticular muscles of the shoulder, elbow, and wrist, and even of the biarticular muscles running along the shoulder and elbow and along the elbow and wrist. This will provide in-depth insight into the coordination of muscles. In the future, ARMANDA can be used to measure the reflexes during movements, which can show us how people can switch smoothly from posture to motion. It is known, for example, that those suffering from Parkinson's disease have trouble doing so.



The LUMC in Leiden houses the POPE machine, a device used to measure the performance of PD patients to control their wrist motion. POPE is a derivative of the test setups at TU Delft, and uses an electrical instead of a hydraulic actuator.

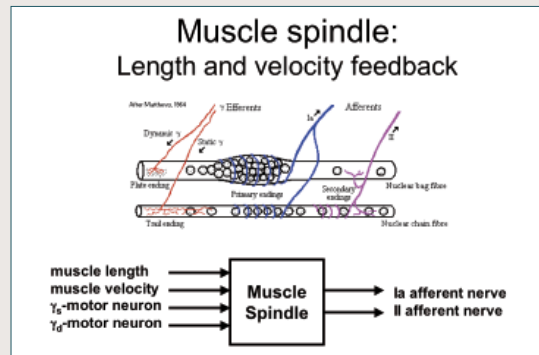


An important component of the Delft research method is the frequency of the force disturbance signal. In high-frequency disturbances (top), the use of reflexes to counteract the disturbance is less efficient for the human body. In low-frequency disturbances (centre) however, test subjects will use their reflexes by

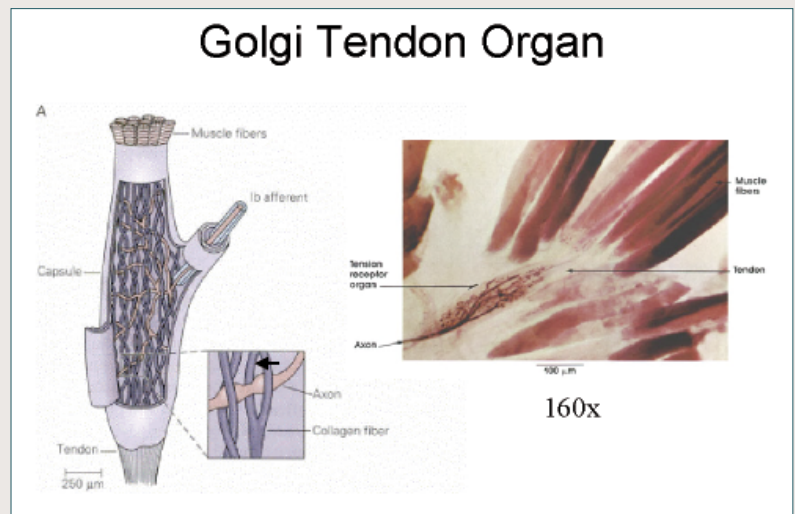
increasing the reflex strength. Highly typical responses are encountered when the disturbance contains only a very limited number of frequencies (e.g. a range of 0.3 Hz) (bottom). In this case the reflex strengths are optimised so they will be effective only within the narrow frequency band. Patients suffering from neurological disorders such as PD, the effects of a cerebral haemorrhage, or Parkinson's disease, are far less able to modulate their reflexes. These tests give us a good idea of the nature of their disorder.

Clinical gap The way reflexes are controlled in the human body is pretty complex. Van der Helm: "Even the medical profession has little or no idea what actually happens when reflexes start going wrong. They tend to look at the symptoms rather than wonder what is actually going on. At a number of meetings I have had with physicians, I started to ask for more details, and so I found out that they too have no idea how some of the reflexes in the human body work. The only way to find out is by making use of methods and insights from the field of mechanical control systems." Therefore the research effort of Delft University within the TREND project is essential for bridging the gap between clinical and mechanical knowledge. Only when we truly know what exactly a reflex pathway is and what it does, will we be able to start looking for a treatment for this problem. However, it will still be a far cry from finding a cure for PD patients. The insight gained from the joint effort of all the researchers united in TREND, from control theory, biochemistry, genetics, and other scientific efforts, will eventually contribute towards finding a way to actually treat PD and possibly prevent it. In other words, the end of a syndrome.

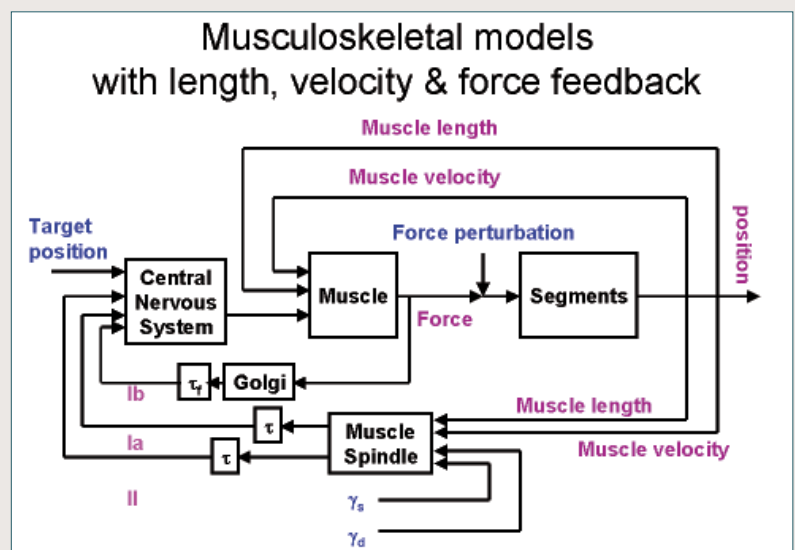
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The muscle spindle is a little sensor located in the muscle that measures the length and contraction speed of the muscle. The muscle spindle is approximately 7 millimetres long, is located parallel to the muscle fibres, and is attached to them. The muscle spindle consists of nuclear bag fibres, which are sensitive to stretching velocity, and nuclear chain fibres, which are sensitive to the muscle's length. The fibres consist of a sensory part at the centre, and very small muscle fibres at the ends. The muscle fibres within the muscle spindle are activated separately from the rest of the muscle, by the γ -motor neurons. As a result the sensor remains sensitive over a wide range of muscle lengths.



The Golgi tendon organ is located at the transition between muscle fibres and the tendon, and consists of nerve fibres interwoven with the tendon fibres. As the tension in the tendon increases, the nerve fibres are compressed, producing a signal. In this way, the Golgi tendon organ records very accurately (to within a few mN) the force within the muscle. The resulting information is sent directly to the central nervous system.



This diagram shows the feedback pathways in the neuromuscular system. A change in the angle of the joint causes the muscle to become stretched. Due to the innate spring-damper properties of the muscle, forces are generated that counteract the disturbance. As the muscle extends, it becomes activated via the reflex pathways, and counteracts the extension. The result is like a delayed-action spring. By incorporating the delay in the calculation and measuring the muscle activation, the muscle's viscoelasticity can be distinguished from the reflexive responses.