What makes tissue soft and yet so tough

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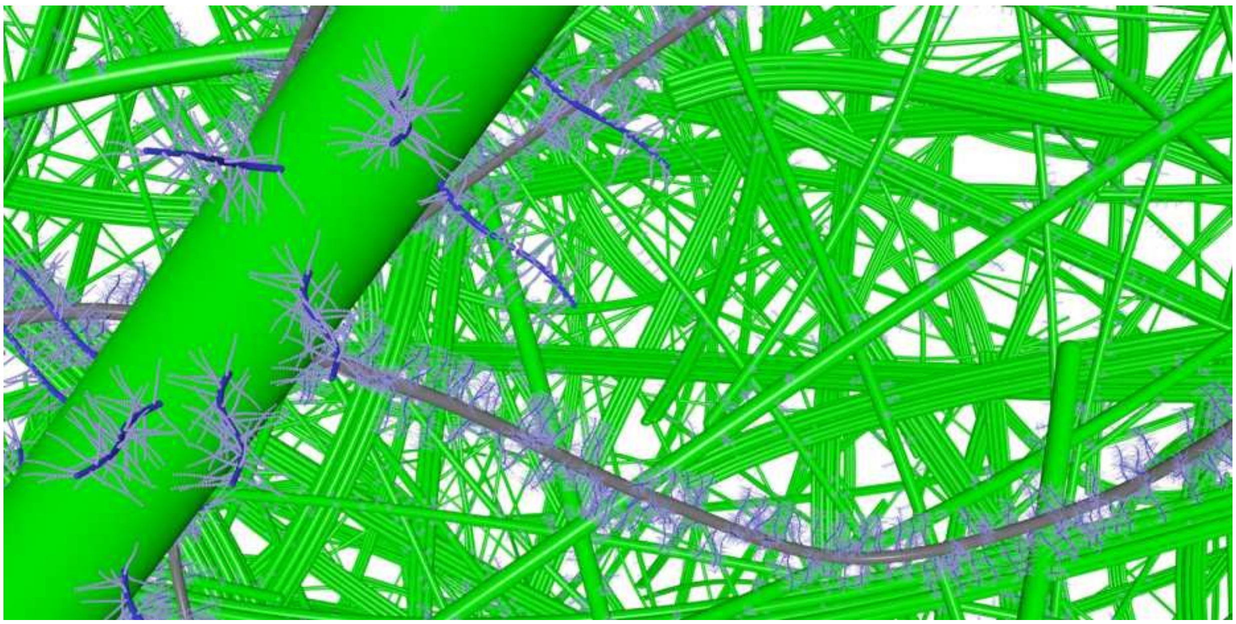

The mechanical behaviour of soft biological tissue in the human body is determined by the interactions between collagen fibres (green), proteoglycans (blue) and water (transparent). Credit: ETH Zurich

Engineers at ETH Zurich have discovered that soft biological tissue deforms very differently under tension than previously assumed. Their findings are already being put to use in medical research projects.

In the womb, the unborn child floats in an amniotic sac filled with amniotic fluid. The baby's smooth development is dependent on this sac remaining intact. However, it is possible for the protective container to tear following interventions such as amniocentesis or foetal surgery – or even spontaneously.

Stretched tissue loses volume

Taking such medical problems as their starting point, researchers in the group led by Edoardo Mazza, Professor at ETH Zurich's Institute for Mechanical Systems, studied how parts of the amniotic sac, and other soft biological tissues, deform under a tensile load. One of their most important – and surprising – findings is that tissue loses mass as it stretches, with a physiological stretch of 10 per cent leading to an average loss of about 50 per cent.

"This contradicts the prevailing paradigm that although such soft biological tissue can deform significantly, its volume remains unchanged," explains Mazza. By taking measurements of tissue samples, his group was able to show that volume is lost due to the fact that liquid stored between cells and collagen fibres in the tissue escapes from the stretched area.

Interaction between mechanics and chemistry

Alexander Ehret, team leader in Mazza's group, and his colleagues used extensive computer simulations to clarify the mechanism responsible for this. The basis is the alignment of collagen fibres in the tissue. The fibres form a sort of three-dimensional network, in which they run in all directions within a plane, showing only slight out of plane inclination.

If this network is pulled, all the collagen fibrils that lie more or less in the direction of pull move closer together in a scissor-like motion, squeezing the fluid out of the tissue. The fibres are undamaged, as they are mainly displaced towards the plane and only slightly stretched.

The volume loss is reversible. When the tissue relaxes again, it reabsorbs water from the surrounding tissue. "The reason is negatively charged macromolecules that are bound firmly to the collagen fibres," explains Mazza. They cause the water to flow back into the tissue according to the principles of osmosis. In experiments, this process can be repeated time and time again.

Putting tissue to the test

This densification of the collagen fibres is extremely useful, particularly in the case of injuries, as the scientists discovered in further experiments: if a taut piece of soft biological tissue is cut a crack is formed, but the collagen fibres then come together at the tip of the tear. "If the tissue is further stretched, this reinforcement is usually enough to prevent the tear from growing," explains Ehret.

The researchers have spent the last decade developing dedicated devices, aids and protocols they use to analyse the mechanical behaviour of soft biological tissues. As a result, they have been able to stretch both large and microscopically small pieces of tissue in one or multiple directions – for example, through inflation. They also succeeded in quantifying the tissue's response and in describing and explaining the observed effects using computer simulations based on algorithms, which they also developed themselves.

Direct medical applications

However, Mazza and Ehret were not only interested in understanding how tissue behaves under a tensile load. "We are engineers," says Mazza. As such, they prefer to work on solutions of real-life problems. The new findings are therefore incorporated directly into tackling specific medical challenges, such as "tissue engineering", the artificial production of biological tissue intended to regenerate or replace damaged tissue in patients.

Based on their new findings, the researchers want to look first at the substrates on which the tissue grows.

"Our aim is to create the most physiologically accurate conditions for the engineered tissue – that is, to imitate nature as closely as possible," says Mazza. He and his colleagues are convinced that cells in growing tissue receive signals from the substrate that then play an important role in determining the properties of the replacement tissue.

The scientists attach a fundamental role to the interaction between chemistry and mechanics. "It is vital that the substrate has the correct properties, including in particular the correct interplay between charged macromolecules and collagen fibres," Ehret explains.

New skin for burn victims

The researchers plan to participate in a project at University Children's Hospital Zurich that aims to cultivate replacement skin for burns victims more quickly and effectively. This collaboration will take place within the framework of the Skintegrity flagship project operated by University Medicine Zurich. The researchers submitted a corresponding project proposal to the Swiss National Science Foundation in late September.

However, Mazza's group is already applying its expert knowledge to a project at University Hospital Zurich that deals with tears in the amniotic sac. This project initially sought to determine the properties required by the tissue in order to repair such injuries. Now, their focus has turned to the question of why these tears occur in the first place. When dealing with this type of questions the engineers feel in their element. "To be able to make a contribution to such medical projects," says Mazza," is highly motivating."

More information: Alexander E. Ehret et al. Inverse poroelasticity as a fundamental mechanism in biomechanics and mechanobiology, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00801-3

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