Measuring what cells feel using the nano-epsilon dot method

When we walk on the sand, a trampoline or a concrete pavement, we can feel the hardness, softness and springiness of the ground and respond by changing the way we move. The way we respond depends on how heavy we are, as well as on the size of our feet. In the same way, cells in our body are also responsive to the mechanical features of the tissues around them, changing their behavior. A good example is that of aged tissues, which are harder and less compliant than younger ones. Cells on stiffer materials which resemble older tissue usually move and grow slowly. Some studies suggest that stiffer and less compliant tissues also inhibit tissue healing and regeneration.

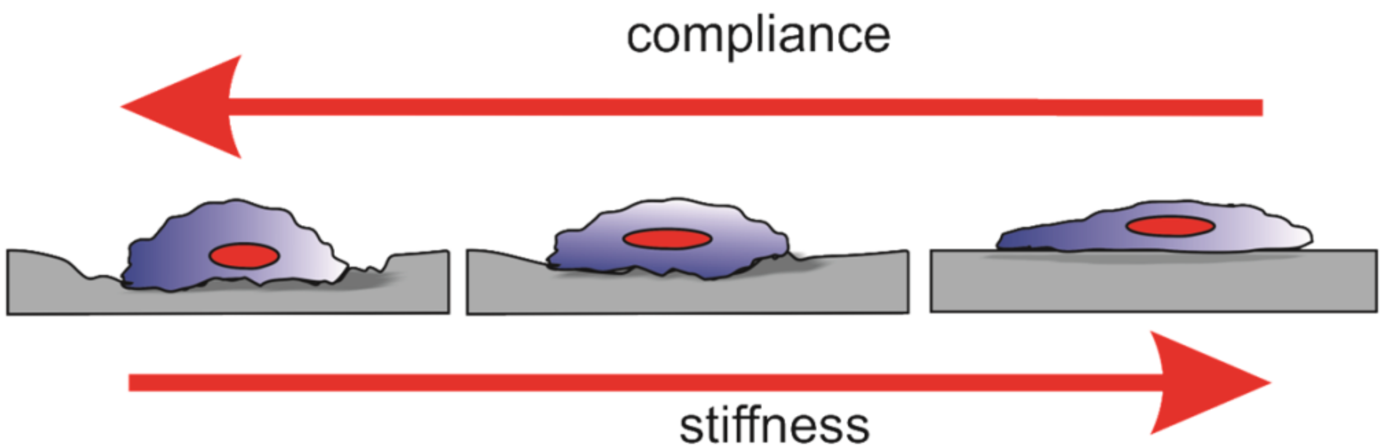

Fig. 1. Cells respond to the softness or compliance and hardness or stiffness of tissues around them.

To better understand what cells feel beneath them, it is important to determine the mechanical properties of tissues and materials at the same scales as cells themselves because larger scale measurements may miss local feature and characteristics. Biological tissues are typical biphasic materials in which a solid network made up of different components (e.g proteins, glycosaminoglycans) is swollen and surrounded by water. Their resultant mechanical behavior is therefore viscoelastic, that is in between that of purely viscous (e.g. water) and elastic (e.g. rubber) materials. The solid part is generally responsible for the elasticity, whereas viscosity arises both from network mobility and the contribution of water and other molecules in the aqueous solution. Viscoelasticity gives rise to time (e.g. creep, stress-relaxation) and frequency or strain-rate dependent material response. For instance silly putty is a typical viscoelastic material: it bounces like a ball when thrown fast, but is pliable when handled slowly. Elastic properties, such as the elastic or Young’s modulus, are not enough to describe the viscoelastic behavior. The latter is generally described using lumped parameter models combining pure springs and dashpots in different configurations. The general model is composed of a pure spring (E_0) in parallel with *n* spring-dashpot arms (E_i -η_i), defining a set of *n* different characteristic relaxation times equal to $\tau_i = \eta_i / E_i$.

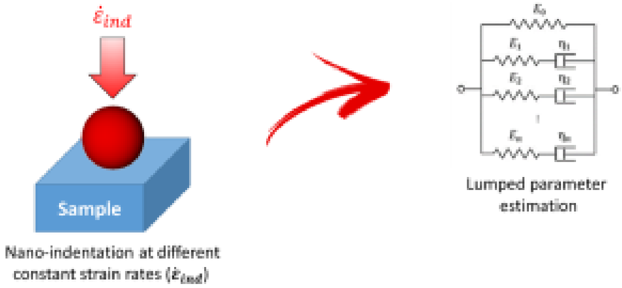

Fig. 2. Schematic of the nano-epsilon dot method. Samples are tested through nano-indentation measurements at different constant strain rates (ε̇_ind). The results are used to derive viscoelastic constants (i.e. Ei and ηi) for lumped parameter models.

Mechanical properties at the microscale are usually measured using nano-indentation, a method in which a small micron-sized indenter is pushed into the surface of a sample and the force required to push a given distance is measured. There are two important novelties in this paper: first, a new mathematical definition of indentation stress (i.e. force per unit area of a round indenter) and strain (i.e. the deformation of the surface as the indenter pushes through it) is derived. Second, it describes a new way to accurately probe the viscoelastic properties of soft materials and tissues through a series of indentation tests performed at different speeds. Unlike conventional nano-indentation, this approach does not require contacting the material before starting the test, which is great for soft tissues that are very sensitive to forces and touch. Combining the two allows the accurate measurement of the mechanical viscoelastic properties of soft materials and tissues, the derivation of spring and dashpot constants for lumped models as well as resultant elastic moduli and characteristic relaxation times.

We use the words "nano-epsilon dot" to describe the new method because epsilon dot (ε̇) is the mathematical symbol for strain-rate or "speed of deformation". The nano-epsilon dot method can be used to measure tissue mechanical properties at typical cell length scales in absence of pre-stress.

Publication

[The nano-epsilon dot method for strain rate viscoelastic characterisation of soft biomaterials by spherical nano-indentation.]

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