Investigating the influence of relative humidity on expression micro-wrinkles.

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Abstract: The quest for efficient anti-wrinkle treatments has mainly focused on biochemical approaches aiming to mitigate or slow down the effects of both intrinsic and extrinsic ageing. However, the biophysical principles that govern the formation and evolution of wrinkles remain to be elucidated. Georges Limbert shares the findings of a study his computational biophysics group conducted with US researchers.

The prospects—and consequences—of ageing are of concern to us all, especially when considering the likelihood of developing wrinkles. They are not only a hallmark of ageing—with its cosmetic and social implications—but also play a fundamental role in how we physically interact with many products and devices, from moisturiser cream and make up, adhesive plasters and incontinence products, to razor and the fabrics of our clothes. Unveiling the underlying biophysical principles that condition the morphologies and patterns of wrinkles are essential in evaluating, and ultimately, predicting, how an ageing or aged skin interacts with its environment. Over the life course, the mechanical and microstructural properties of the skin play a fundamental role in conditioning its mechanical response (Limbert, 2017), particularly with regards to contact interactions, where friction is pivotal. Skin friction is a complex multi-factorial phenomenon (Adams et al., 2007; Leyva-Mendivil et al., 2017a; Leyva-Mendivil et al., 2017b; Leyva-Mendivil et al., 2017c) which, if excessive, could have detrimental effects on skin integrity (i.e. skin tears) (Morey, 2007). Any alteration of the skin surface (e.g. wrinkles), particularly at the microscopic scale, is likely to modulate these effects (Derler and Gerhardt, 2012; Limbert, 2017; Veijgen et al., 2013). Moreover, because ageing wrinkles are generally correlated with change in the physical, material and structural properties of the subjacent microstructural skin layers (Assaf et al., 2010; Ramos-e-Silva and da Silva Carneiro, 2007), the frictional response of the skin is highly dependent upon wrinkle characteristics.

There is evidence that ageing wrinkles (Piérard et al., 2004) do not arise from the emergence of new skin structures but are merely a manifestation of alterations in the material and structural properties of the skin induced by intrinsic and extrinsic ageing (Kligman et al., 1985; Pond et al., 2018). *Expression (or temporary) wrinkles* (also called *expression lines*) are typically associated with facial skin movement and are rather macroscopic in nature. They can originate from facial muscular activation (i.e. smiling) or by mechanical actions on the skin surface such as twisting, shear or compression. Dynamic wrinkles at a smaller scale, that of skin microrelief—henceforth, referred as *micro-wrinkles* (MW)—are particularly relevant to skin friction as they modulate surface deformation and short-range electromagnetic interactions that control adhesion (Israelachvili, 2011), an essential component of friction. Skin microrelief is made of a network of furrows and ridges—also called *sulcus cutis* or glyphic patterns—criss-crossing each other and thus delimiting polygonal plateaux with rectangular, square, trapezoidal and triangular shapes. These polygonal patterns—present at birth—lose their isotropic (i.e. properties are the same in any direction) distribution with age and become more anisotropic (i.e. properties are direction-dependent) by forming preferred structural orientations (Piérard et al., 1974). The characteristics of skin microrelief can be classified according to the orientation and depth of featured lines into primary, secondary, tertiary and quaternary lines (Hashimoto, 1974; Lévêque, 1999; Piérard-Franchimont and Piérard, 1987; Piérard et al., 1974).

Because water molecules chemically and physically interact with the skin constituents, particularly with the *stratum corneum*, moisture levels in our skin play a major role in the development and evolution of wrinkles. As relative humidity drops, this outer layer becomes dryer and stiffer. When this happens, the micro-wrinkles at the surface of the skin, induced by facial muscle actions, become much deeper, larger and, therefore, more visible. This can happen in a matter of a few hours (e.g. in a dryer environment such as a heated room or an aircraft cabin during a long-haul flight) so the immediate answer—and one we all know—is to keep our skin hydrated in order to minimise the creation of micro-wrinkles.

To date, developing innovative and effective solutions for the prevention and treatment of wrinkles has mainly focused on biochemical approaches (i.e. cream). Recently, our computational biophysics group in Southampton and that of Prof. Ellen Kuhl, who heads the Living Matter Lab in the Mechanical Engineering Department at Stanford University (USA), have developed a quantitative physics-based approach to understand how alterations in the mechanical properties of the *stratum corneum* through variations in relative humidity levels condition the geometrical characteristics of micro-wrinkles (Limbert and Kuhl, 2018).

The work hypothesis underpinning this study is that the characteristics of micro-wrinkles are determined by either the natural skin microrelief topography (i.e. geometry) or the ratio of stiffness (i.e. mechanical properties) between the *stratum corneum* and the underlying layers (i.e. viable epidermis an dermis), depending on the magnitude of this stiffness ratio.

In our biophysical modelling approach, the skin was modelled as a multi-layer structure featuring a 20 µm thick *stratum corneum* laying on top of a much thicker substrate representing the viable epidermis and dermis. The partial differential equations that govern the mechanical behaviour of the skin (i.e. mathematical relationships linking deformations to applied forces) were solved for the whole skin structure using a computational technique called the Finite Element Method (Zienkiewicz and Taylor, 1989) which is widely in engineering (e.g. aerospace), and, has become a method of choice for applications in the life sciences. To mimic the formation of expression micro-wrinkles, in-plane compression of the skin was simulated for six different scenarios, each corresponding to a maximum to low relative humidity level. The ratio of stiffness between the *stratum corneum* and the underlying skin layers α was varied from 1 (i.e. maximum humidity and minimum stiffness of *stratum corneum*), through 20, 100, 200, 400 to 600 (i.e. minimum humidity and maximum stiffness of *stratum corneum*). The stiffness of *stratum corneum* was used as a surrogate measure of relative humidity (Levi and Dauskardt, 2010; Levi et al., 2010; Wu et al., 2006).

Results of the computational analyses highlighting the differences in wrinkle characteristics depending on relative humidity level in the *stratum corneum* are presented in **Figure 1**. Upon application of compressive forces, peaks and valleys on skin microrelief are magnified or switched into valleys and peaks. For moderate α values (≤ 100), secondary lines of skin microrelief act as geometrical imperfections that trigger wrinkle formation. As α increases, these imperfections (including those represented by primary lines) become less dominant on wrinkle wavelength. Zones of compressive and tensile strains also get progressively realigned along the direction normal to that of the applied compressive force which induces wrinkling. There is a clear correlation between the spatial frequency and amplitude of wrinkles and the ratio of stiffness α. More in-depth analyses of the results can be found in the original paper (Limbert and Kuhl, 2018). It is also noteworthy that, despite its extreme thinness, the *stratum corneum* plays a key role in determining the characteristics of skin micro-wrinkles, even in younger people. Here, the interplay of mechanics and geometry is crucial.

Naturally, the skin is a much more complex system than what our model captures. After all, a mathematical model is, by definition, a caricature of a physical reality. However, mathematical models implemented under the form of computer simulation programmes offer scientists and engineers practical quantitative tools to systematically and efficiently compare various physical scenarios or study the effects of particular parameters on a system response. For example, in this study we have developed a computational model that sheds light on the potential role of *stratum corneum* stiffness in relations to the mechanical properties of the underlying layers on the geometrical characteristics of expression micro-wrinkles. As this model gets refined with the addition of new experimental data, and gets incrementally validated against physical observations, its potential will become more widely recognised, particularly in industrial circles. Ultimately, such a model will provide a rational and science-based approach to design innovative, preventive, and longer-term treatment solutions that could delay and mitigate the effects of ageing on our skin. Our team in Southampton and collaborators at the Universities of Glasgow and Cape Town have already started the development of physics-based models of ageing (Pond et al., 2018) that model how skin ageing affects the mechanical and microstructural properties of the skin. The next step is to couple this modelling framework to our skin wrinkle simulator.

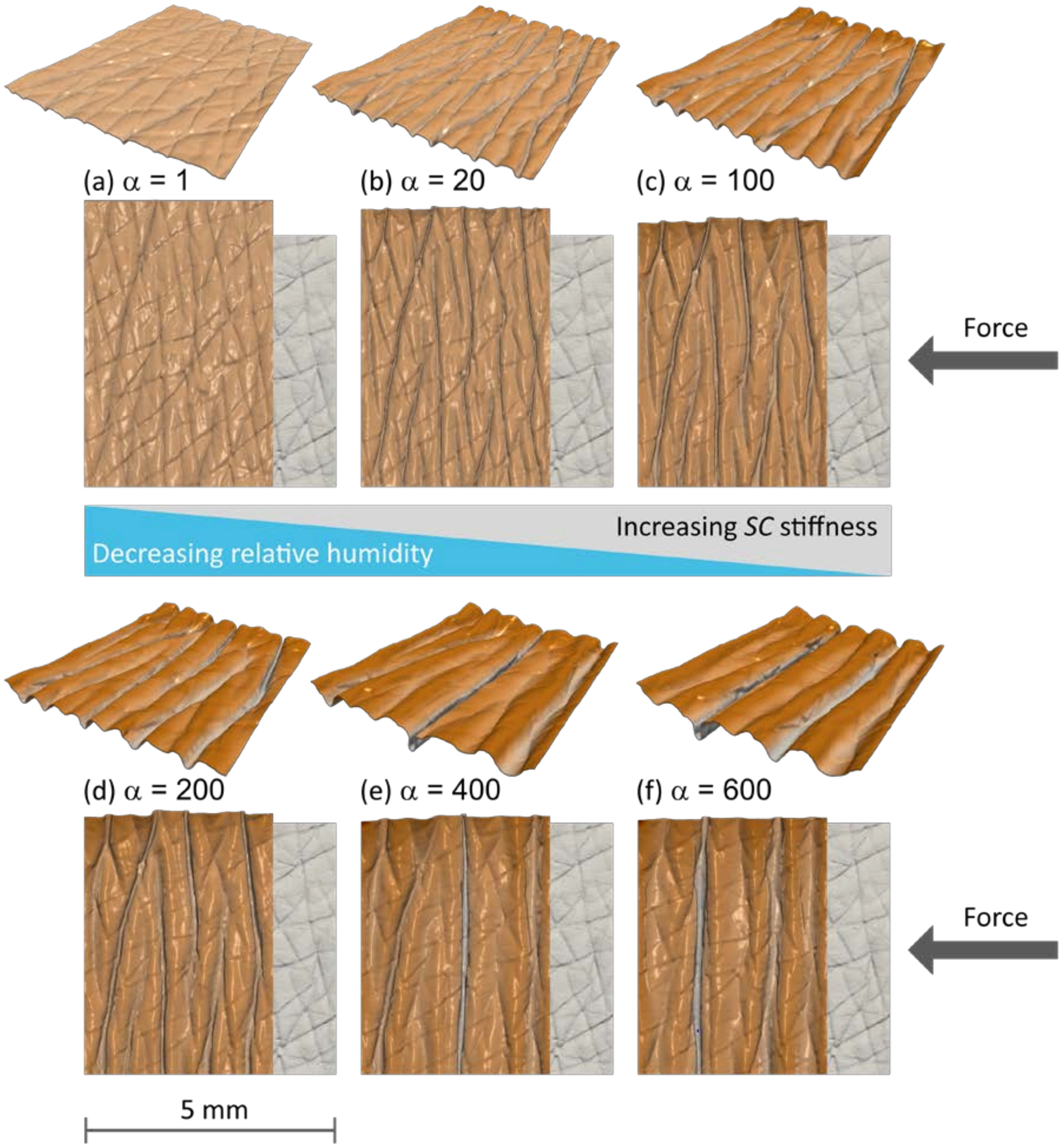

Figure 1. Deformed shape of the 20 μm uniformly-thick *stratum corneum* (*SC*) as a function of stiffness ratio α (inversely proportional to hydration level of *stratum corneum*) following a 25% macroscopic uniaxial compressive force (indicated on the schematic). For each row, (a-b-c) and (d-e-f), a three-dimensional view of the *deformed stratum corneum* layer is provided (top) while a top view (i.e. above the skin surface) highlights the change in geometry of the wrinkled skin compared to that of the original *undeformed* skin surface (coloured in white).

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