Lessons learned from the exquisite design of the endothelial surface glycocalyx and their amazing applications

Q. Wu, Y. Andreopoulos & S. Weinbaum
Departments of Biomedical and Mechanical Engineering & New York Center for Biomedical Engineering, The City College of the City University of New York, USA

Abstract

In a recent paper by Weinbaum et al. [1], a theoretical model was developed for the structural organization and function of the thin 0.4 μm endothelial surface matrix layer of proteoglycans and glycoproteins that coats the inner lining of our blood vessels. In particular, it is shown that the core proteins in this layer are sufficiently stiff to serve as an exquisitely designed transducer of fluid shear stress to the cortical cytoskeleton of the endothelial cell in initiating intracellular signaling, but offer negligible resistance to buckling when red cell motion is arrested. This latter property allows highly flexible red cells to move through tightly fitting capillaries with remarkably little frictional resistance since the normal force is balanced nearly entirely by the fluid pressure in the highly compressible glycocalyx layer and sliding friction between the cell and the solid phase is vanishingly small. We first show that there is a remarkable dynamic similarity between the motion of red cells gliding on the endothelial glycocalyx and a human snowboarding on fresh powder although they differ in mass by $10^{15}$. One is able to produce lift forces in each case that are four orders of magnitude larger than classical lubrication theory due to the inability of the trapped fluid or air in the porous layer to rapidly escape. These concepts are then extended to the design of a future generation train that can glide on a track whose permeability and elastic properties are similar to goose down.

Keyword: endothelial surface glycocalyx, red cell, snow, skiing, train track.

1 Introduction

Two recent papers, Weinbaum et al. [1] and Feng and Weinbaum [2], have demonstrated the quantitative feasibility of generating lift forces on soft porous
media which vastly exceed those currently available in traditional lubricating films and also dramatically reducing the drag due to sliding friction. These concepts deduced from the motion of red cells in capillaries are applied in this paper to measure for the first time the dynamic pore pressures and lift forces generated during skiing and to design a new type of high speed train track which can support gliding vehicles weighing 50 or more metric tons with extremely low sliding friction.

Biological scientists have wondered, since the motion of red cells was first observed in capillaries, how the highly flexible red cell can move with so little friction in tightly fitting microvessels. In 1996 Vink and Duling [3] conclusively demonstrated in vivo that our microvessels are lined with a uniform highly compressible endothelial surface layer (ESL), a glycocalyx of glycoproteins and proteoglycans which varies in thickness from 150nm in frog mesentery capillaries (Squire et al. [4]) to 400nm in hamster cremaster microvessels [3]. In Fig. 1 we have sketched a proposed ultrastructural model [2,4] for the 3D organization of the ESL and its linkage to the underlying actin cortical cytoskeleton of the endothelial cell. This model has been deduced from an autocorrelation analysis of electron micrographic images of the ESL and its underlying cortical scaffold. Two periodicities are observed, a 20 nm periodicity for the spacing of the core proteins and the scattering centers that are aligned along the axes of the core proteins, and a 100 nm periodicity associated with the spacing of each bush like core protein cluster. The latter is believed to arise from root like connections to an organized actin filament network beneath the membrane.

Vink and Duling also observed that when red cells were travelling at velocities $> 20\mu m/s$ they appeared to glide above the ESL and there was a narrow intervening fluid gap. However, at velocities $< 20\mu m/s$ the red cells entered the ESL and when motion was arrested the red cells crushed the glycocalyx and filled nearly the entire lumen of the capillary. Subsequently, hydrodynamic models were developed to account for the ESL and describe the flow and pressure field between the red cell and endothelial membranes provided the cells did not enter the ESL, Damiano [5] and Secomb et al. [6].

In [2], Feng and Weinbaum develop a generalized lubrication theory to describe the pressure and lift forces generated when the red cell enters the ESL. This theory describes a one or two-dimensional planar surface sliding on top of a highly compressible porous media in which the normal forces generated by the solid phase are negligible. Feng and Weinbaum show there is a remarkable dynamic similarity between a red cell gliding on the glycocalyx and a human snowboarding on fresh snow powder although they differ in mass by order $10^{15}$.

In each case the flow in the porous layer is described by effective medium theory (Brinkman equation) [7] in which the local value of the Darcy permeability $K$ varies with compression. The analysis shows that the behavior is governed by three dimensionless groups, a dimensionless permeability parameter $\alpha = h/K^{1/2}$, where $h$ is the thickness of the porous layer, the slope $\lambda$ of the planning surface and its length to width ratio $L/W$. For classical lubrication
theory $\alpha = 0$. This model was then applied to a red cell with a flexible membrane, but with a uniform value of $K$ (Secomb et al. [8]).

The analysis in [2] illustrates several basic new concepts. First, if the planing surface does not have lateral edges, such as a red cell where $L/W = 0$ since the capillary wall completely surrounds the red cell, the lift forces increase as $\alpha^2$ for all $\lambda$ for $\alpha \gg 1$. Thus, huge increases in lift can be generated on the time scale of the passage of the planar surface if the fluid/air is unable to effectively drain from the porous media beneath it. Using the model for the glycocalyx structure shown in Fig. 1, Weinbaum et al. [1] estimate that for the ESL $K = 3.2 \text{ nm}^2$ and $\alpha = 225$ if $h = 0.4 \mu\text{m}$. Large increases in pressure would develop beneath the red cell membrane were it not for the fact that $\lambda << 1$. For snowboarding the experiments presented herein show that $\alpha$ is of order $10^3$ or larger. Thus, enormous lift forces would be produced were it not for the fact that the temporarily trapped air beneath the snowboard can escape at its lateral edges. The analysis in [2] shows that the maximum pressure that can be generated will decrease by a factor $(W/L)^2$ due to this lateral leakage and, thus, substantially reduce the potential maximum lift. Despite this leakage limitation, the analysis in [2] predicts that a snowboarder moving at speeds in excess of 10 m/s can easily float on the air trapped within the snow layer.

The ultrastructural model sketched in Fig. 1 is used in [1] to explore the structure and function of the core proteins in the ESL as a possible mechanotransducer of fluid shear stress to the actin cortical cytoskeleton of the cell. To determine the bending rigidity $EI$ of the core proteins the authors develop an elastohydrodynamic model to quantitatively explain the time dependent restoration of the ESL after it has been crushed by the passage of a leukocyte Vink et al. [9]. This model predicts that $EI$ for the core proteins, 700 pN·nm², is about 1/20 that of F-actin. The elastic buckling forces on the core
proteins during red cell arrest are then compared with the hydrodynamic pressure forces produced by the time dependent drainage of the trapped fluid between the red cell and endothelial cell membranes. One finds that for this value of $EI$ the core proteins are sufficiently stiff to withstand large bending deformations due to fluid shear acting at their tips at physiological shear rates, and thus act as a mechanotransducer of fluid shear, but insufficient to resist buckling during red cell arrest. The latter resistance derives primarily from the drainage pressure of the transiently trapped fluid which is shown to be two orders of magnitude greater than the elastic buckling force of the core proteins.

For snow it is well known that sliding friction in skiing is greatly reduced by the presence of μm thick fluid films that form beneath the ski due to frictional heating (Colbeck [10]). This film greatly reduces friction drag in cross-country skiing much like the thin fluid film that exists between the red cell membrane and the edge of the ESL when the red cell is moving at velocities $> 20 \mu$m/s. For red cell velocities $< 20 \mu$m/s the microcirculation has had to devise another way of greatly reducing its frictional drag during red cell arrest and start up. The force $D$ due to sliding contact friction is usually written in the form $D = \nu N$, where $\nu$ is the coefficient of sliding friction and $N$ is the normal load due to the solid phase. The ESL must constantly restore itself after either the passage of a white cell or the arrest of a red cell and, thus, the fibers comprising the ESL must be capable of a small restoring force $N$. However, as noted above this normal force exerted by the core proteins is only a tiny fraction of the force due to the pore pressure and, thus, the friction drag from the solid phase will be dramatically reduced since most of the load is carried by the fluid. In our train track application that is described later, one would like to design a synthetic material that has the properties of loosely packed goose down, namely a permeability that is comparable to snow, but have a very weak restoring force that allows for slow restoration of the porous layer after compression, like the ESL.

2 Snow compression

While it would be very difficult to measure the excess pore pressure that develops during red cell arrest an equivalent experiment can be easily performed for snow. To our knowledge no one has ever attempted to measure the draining pressure that builds up in snow on a time scale characteristic of skiing or snowboarding. There is an extensive literature on the behavior of snow during uniaxial compression, as summarized in Mellor [11] and Shapiro et al. [12], but these studies examine the compression of snow and its creeping behavior on time scales much longer than of interest herein. In Fig. 2 we have sketched a novel piston-cylinder apparatus with rigimesh sidewalls which will filter snow crystals whose size is greater than 0.120 mm. The mesh is a sintered arrangement of screens with negligible airflow resistance. The piston and a probe mounted on the bottom plate are instrumented with high-frequency, sub-miniature pressure transducers fabricated by Kulite Semiconductor Products. These transducers are able to measure millisecond variations in dynamic pore pressure on the underside of the piston and on the centerline of the cylinder when a weighted piston is
dropped from rest. The diameter of the piston, 40 cm, is chosen to be representative of the dynamic response that one would encounter while snowboarding. The electrical output is collected with an Iotech 488/8 data acquisition system and finally transferred to a computer to be recorded.

![Figure 2: Schematic of dynamic snow compression apparatus.](image)

In Fig. 3A we have plotted the results for the time dependent variation of the pore pressure at the location of the central pressure transducer on the underside of the piston after it is released from rest. Natural snow, two days old, with an ambient temperature of –10ºC was used in this experiment. One observes a rapid rise in pore pressure within 0.1 seconds and then a decay that occurs on a time scale of roughly 0.5 seconds. In contrast, the length of time that a 1.5 m snowboard would be in contact with a given patch of snow if it was travelling at 10 m/s would be 0.15 s. It is clear from the figure that after 0.15 s the excess pore pressure has only started to relax and much of the weight of the snowboarder would be supported by the air that is still trapped in the partially compressed snow layer. The solid curves in the Fig. 3A are our theoretical model predictions for the time dependent decay of the excess pore pressure, where the change of the Darcy permeability of snow as a function of compression is based on Shimitzu’s empirical relationship [13]. One notes that there is one value of the initial Darcy permeability $K_0$, $5.0 \times 10^{-10}$ m$^2$, which provides a best fit to the experimental data. This theoretical model is briefly described below.

A balance of forces acting on the piston requires that
\[ m \frac{d^2h}{dt^2} = -mg + F_{\text{air}} + F_{\text{max}}, \]  

(1)

where \( m \) is the mass of the piston and \( h \) is its instantaneous height. The pressure distribution beneath the piston is determined by its instantaneous velocity and the solution of a Poisson equation for the Darcy flow within the cylinder. \( F_{\text{air}} \) is the surface integral of this pressure field. \( F_{\text{snow}} \) is the force exerted by the solid phase. The latter determined by an independent experiment in which the piston is loaded slowly and incrementally, so that the excess pore pressure is negligible, to its final weight \( mg \). One finds that the force due to the solid phase during compression approximately satisfies an equation of the form

\[ \frac{F}{F_{\text{max}}} = f\left( \frac{\Delta h}{\Delta h_{\text{max}}} \right). \]  

(2)

where \( F_{\text{max}} = mg \) and \( \Delta h_{\text{max}} \) is the final displacement of the piston when the full load \( mg \) is applied. If one plots the time dependent variation of the inertia, pore pressure and solid phase forces in eqn (1) scaled by the weight of the piston, one finds that after an initial rapid transient the inertia of the piston is negligible and the weight of the piston is supported by the pore pressure and the load bearing stress of the solid phase. Eqn. (2) is highly non-linear for both snow and goose down. When \( \Delta h/\Delta h_{\text{max}} < 0.3 \) the force exerted by the solid phase is small, whereas when \( \Delta h/\Delta h_{\text{max}} \) approaches unity the excess pore pressure has been drained and the solid phase supports the entire load.

Figure 3A: Time-dependent pressure at the center of the piston and its comparison with the theoretical prediction of eqn (1) during the dynamic compression experiment with snow using the porous cylinder-piston apparatus. The applied load is 5.9kg, the initial height of the porous layer \( h_0=11.43 \text{cm} \), \( \Delta h_{\text{max}}/h_0=0.22 \), \( P_{\text{max}}=1240 \text{Pa} \).
3 New concept for train track

The behavior just described suggests that it might be possible to support very heavy loads on very soft porous materials provided the time of passage of the planing surface is small compared to the time that it would take the confined air or fluid to drain from the porous media beneath it. The calculations in Fig. 15 of [2] show that the air trapped in snow can easily support the weight of a 70kg snowboarder when $K_0$ lies in the range $10^{-8}$ to $10^{-9}$ m$^2$. For a snowboard whose surface area is 0.5 m$^2$ the pore pressure required is approximately 1/75 of an atmosphere or 1.4 kPa. The value of $K_0$ required will depend on the velocity and slope $\lambda$ of the snowboard. The feasibility of supporting a 50 ton high speed train car whose planform is 25 m long and 2 m wide can be gleaned from the fact that the average excess pore pressure required will be 9.8 kPa or only seven times that of the snow board. This is easily realizeable for a porous material whose permeability is of order $10^{-8}$ m$^2$ or smaller provided the loss of pressure through lateral leakage is eliminated. Furthermore, if the deformation of the solid phase is small, that is $\Delta h/\Delta h_{\text{max}} << 1$, the load bearing force of the solid phase will be small and sliding friction greatly reduced. We shall now show that a synthetic material with the permeability and elastic properties of goose down is ideal for these purposes. This material has the additional important advantage that after compression it has a weak restorative force in contrast to snow which has no elastic recoil.

To measure the dynamic compression properties of goose down, we have used the same porous cylinder apparatus shown in Fig. 2. These results, which are analogous to those just described for two-day old snow, are shown in Fig. 3B. One observes again that there is one value of $K$, 1.6 x10$^{-8}$ m$^2$, which provides a best fit of the experimental data. The principal difference between the curves in Figs. 3A and 3B is that there is no extended relaxation phase for the goose down since the dimensions of the piston are too small and the value of $K$ too large for the excess pore pressure to support most of the piston weight. This behavior is very similar to that observed for freshly fallen snow in the present apparatus where the value of $K$ is similar to that just estimated for goose down in Fig. 3B. The theoretical predictions in Fig. 3B assume that once the piston has reached its maximum compression the recoil force of the goose down is very small and can be neglected.

In Fig. 4 we show a schematic of our proposed lift enhanced, goose down filled train track. The top surface on which the planform glides is a highly flexible porous sheet through which the pore pressure in the porous medium is transmitted. To prevent lateral leakage of pressure the sidewalls of the track are made of an impermeable membrane which is supported by rigid sidewalls. The only significant leakage of pressure occurs at the front and back ends of the planform where the pressure is that of the ambient air. At low speeds, when the velocity of the train car is not sufficient for its weight to be supported by the trapped air in its long slender rectangular shaped goose down pillow, one resorts to wheels. Once the speed has increased to a value sufficient to support the car, the wheels are raised.
Figure 3B: Time-dependent pressure at the center of the piston and its comparison with the theoretical prediction of equation (1) during the dynamic compression experiment with goose down using the porous cylinder-piston apparatus. The applied load is 6.4kg, the initial height of the porous layer $h_0=12.77\text{cm}$, $\Delta h_{\text{max}}/h_0=0.35$, $P_{\text{max}}=400 \text{ Pa}$.

Figure 4: Sketch of the new train model in transverse plane (not to scale).

The performance of our enhanced lift 50 ton train car is plotted in Fig. 5. These theoretical predictions are based on the solution of the generalized Reynolds equation (2.25) in [2] and a track height $h_2$ at the leading edge of 10 cm. $K$ in our experiments is based on goose down from inexpensive pillows with larger more porous feathers. One observes that even for this coarser goose down, where $K = 1.6 \times 10^{-8} \text{ m}^2$, the ratio $k = h_2/h_1$ of the leading to trailing edge heights
will be $< 1.4$ if the car velocity is $> 10$ m/s. Moreover, the performance curves are highly non-linear and at high speeds in excess of 35 m/s there is less than a 10 percent compaction of the track at the trailing edge. For such small compressions sliding friction should be very small since the force exerted by the solid phase will be orders of magnitude less than the force due to the air pressure beneath the planform.

![Figure 5](image-url)

**Figure 5:** The velocity $U$ required to support a train car whose weight is 50 metric tons gliding on a porous track as a function of the compression ratio $h_2/h_1$ for different values of the permeability $K$. Note that very small compressions of the track are required at high velocities $U$. The length of the train car is 25m, its planform width is 2m, and the thickness of the undeformed porous layer $h_2=0.10m$.

In summary, it is amazing to fluid mechanicians who have grown up in a world where dynamic similarity is governed by a Reynolds number to envision that there can be dynamic similarity in the motion of a train whose mass is $10^3$ times that of a human and a red cell which is again $10^{15}$ times smaller. This paper is a beautiful example of how the evolutionary design of nature can transcend many orders of magnitude.

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**References**


