The Casimir Effect in Biology: The Role of Molecular Quantum Electrodynamics in Linear Aggregations of Red Blood Cells

K Bradonjić
Physics Department, Boston University, Boston MA USA

J D Swain
Physics Department, Northeastern University, Boston MA USA
International Institute for Biophysics, Neuss, Germany

A Widom
Physics Department, Northeastern University, Boston MA USA

Y N Srivastava
Physics Department, Northeastern University, Boston MA USA
Physics Department & INFN, University of Perugia, Perugia Italy
E-mail: john.swain@cern.ch

Abstract. Despite the fact that red blood cells carry negative charges, under certain conditions they form cylindrical stacks, or “rouleaux”. It is shown here that a form of the Casimir effect, generalizing the more well-known van der Waals forces, can provide the necessary attractive force to balance the electrostatic repulsion. Erythrocytes in plasma are modelled as negatively charged dielectric disks in an ionic solution, allowing predictions to be made about the conditions under which rouleaux will form. The results show qualitative agreement with observations which suggest that the basic idea is worth further pursuit. In addition to revealing a mechanism which may be widespread in biology at the cellular level, it also suggest new experiments and further applications to other biological systems, colloid chemistry and nanotechnology.

1. Introduction
Casimir forces between objects typically rise faster with decreasing separation than electrostatic forces raising the possibility that at sufficiently small distances they become dominant. We show by an explicit example that the aggregation of red blood cells is a biological situation which can be understood as an interplay between Casimir attraction of plate-like objects (red blood cells) and their mutual electrostatic repulsion. Once the idea is accepted that Casimir forces may play a role in biology, a whole new window on biological phenomena at the cellular level opens up, as well as the possibility of novel new experiments on the Casimir effect in liquid media.
2. Rouleaux Formation
It has been observed for many years that, under certain conditions, erythrocytes (red blood cells) form cylindrical stacks known as “linear aggregations”, or “rouleaux”[1], sketched in figure 1. Each cell is a biconvex discoid (a disc whose opposite faces have been pushed together, forming indentations on each side), with a radius of some 6-8 \( \mu \text{m} \). The maximum thickness near the edges is about 1 \( \mu \text{m} \) and the minimum at the centre is about a third that. One may view blood as an ionic plasma in which red blood cells, and some other cellular colloidal particles, are suspended. Employing direct measurements of colloidal particle mobility, the red blood cells have been shown to carry a net negative charge[2].

A long cylindrical stack of negatively charged red blood cells is shown schematically in figure 1. Attractive forces must exist in order to stabilize the rouleaux formation against the explosion which would take place if only the repulsive Coulomb interaction were existent[1],[2]. Our purpose is to argue that quantum radiation field Casimir forces provide the required rouleaux stability mechanism. The Casimir effect generalizes the well-known van der Waals forces by including electromagnetic retardation effects [3]. Casimir forces are simpler in nature than the selective long range dispersion forces suggested by Fröhlich[4, 5].

The essential physical principles underlying the Casimir forces are quite simple. When electromagnetic radiation interacts with condensed matter, the frequencies of the normal modes are Lamb shifted (though the use of the term “Lamb shift” is not so often used in the context of effects due to boundary conditions). Frequency shifts imply a change in the electromagnetic field free energy. In particular, at virtually zero temperature, the ground state zero point energy changes. A special case of such an energy shift may be found from the electromagnetic modes located between two parallel highly conducting plates. The energy shift then describes an attractive force between two plates and can be understood as being due to the change of zero-point modes when the distance between the plates is changed. The closer the plates, the more reduced is the vacuum energy and the greater the attractive force between the plates[3].

Figure 1. Although each red blood cell or slab has a net negative charge, in certain ionic surroundings the blood cells nevertheless tend to come in stacks or rouleaux structures. Such a stack is schematically drawn above. Despite their apparent closeness, each cell is strongly biconvex and the centres are significantly more separated than this view suggests.
3. Charged Dielectric Plates in an Ionic Solution

For the problem at hand, we consider two dielectric plates each having cross sectional area $A$ and a dielectric constant $\varepsilon_1$. Between the two dielectric plates is a plasma medium of thickness $d$ and dielectric constant $\varepsilon_2$[6]. The zero point electromagnetic field energy per unit plate area is calculable. If the dielectric plates both have a surface charge per unit area $\sigma$, then the electrostatic potential energy density may also be computed taking into account the Debye screening effects of a background plasma solution of ionization strength[1] $I$. It is assumed in both calculations[7] that $d^2 << A$. The final result for the total free energy per unit area $u$ as a function of plate separation $d$ may be written[8]

$$ u(d) = \frac{\sigma^2 A}{2\varepsilon_2} \left[ e^{-d/\Lambda} - \left( \frac{\pi^2 \hbar \sqrt{\varepsilon_0 \varepsilon_2}}{360 \sigma^2 \Lambda} \right) \frac{1}{d^3} \right], \quad (1) $$

The length $\Lambda$ describes electrolytic Debye screening and $\nu$ is a sort of reflection coefficient $\nu = c[(\varepsilon_1 - \varepsilon_2) / (\varepsilon_1 + \varepsilon_2)]^2$. The first term on the right hand side of Eq.(1) describes the Coulomb repulsion between red blood cells while the second term on the right hand side of Eq.(1) describes the Casimir attraction between red blood cells. The relative strength of the two effects is quantitatively described by the dimensionless parameter

$$ a = \left( \frac{\pi^2 \hbar \sqrt{\varepsilon_0 \varepsilon_2}}{360 \sigma^2 \Lambda^4} \right) \left( \frac{\pi^2 \hbar c \sqrt{\varepsilon_0 \varepsilon_2}}{360 \sigma^2 \Lambda^4} \right) \left( \frac{\varepsilon_1 - \varepsilon_2}{\varepsilon_1 + \varepsilon_2} \right)^2 \quad (2) $$

where the Debye screening length $\Lambda$ is related to the ionization strength $I$ via $\Lambda^2 = \{\varepsilon_2 k_B T / e^2 \bar{I}\}$. The ionization strength in physical units is $\bar{I} = \sum n_a z_a^2 |e|$, where $n_a$ is the number of ions per cubic meter having an ionic charge $z_a |e|$. In chemical units of moles per liter, one employs the ionization strength $I = [10^{-3} \text{meter}^3 / \text{liter}] (\bar{I} / N_A)$ where Avogadro’s $N_A$ is the number of ions per mole.

The above theory assumes that the parallel plates are maximally overlapping. If the plates were to slide over one another yet remaining parallel but not maximally overlapping, then the energy would be increased. Thus, there is a force parallel to the plates tending to pull them back into a maximally overlapping state. This force represents a lateral Casimir effect (See, for example, references in [9] which deal with Casimir forces between corrugated planes. The case here is somewhat different, as it deals with finite plates, but certainly one expects an increasingly negative Casimir energy as the plates become more and more close to maximally overlapping[10]). It is centrally important in the context of the rouleaux formation problem since it supplies a force which will tend to align two plates so that they directly face each other with the largest possible area overlap. When many plates are stacked in a cylinder, the lateral force tends to give the cylinder transverse structural stability. With regard to compression stability, one must find a local minimum in the free energy per unit area $u(d)$ with respect to the distance between the plates. A meta-stable equilibrium distance between plates arises from the local minimum at $d_0$ found from equating the force per unit area to zero; i.e. $u'(d_0) = 0$. There exists a critical parameter $a_c \approx 1.57$ such that a local rouleaux minimum exists if $a < a_c$, and a local rouleaux minimum does not exist if $a > a_c$. The resulting free energy per unit area $u(d)$ is plotted in figure 2 for several values of $a$.

4. Comparison with Data

We fix the parameters in the model so that the plates correspond to erythrocytes (relative dielectric constant of 1.1857 and a charge density of 3500 esu/cm²[1, 2] and nominal physical spacings observed of about 1 µm measuring between the centres of the cells) and work at room temperature. This leaves the ionic strength ($I$) and the permeability of the blood plasma relative
Figure 2. The variation of the free energy per unit area with the separation distance. The rouleaux formation can exist at the local minimum only if the parameter \( a \) in Eq.(2) is sufficiently small.

Figure 3. The phase diagram showing the regions in which room temperature rouleaux formations are stable and in which regions such rouleaux formations are unstable. The reference ionization strength \( I_0 = 0.05 \text{ moles/liter} \) has been employed.

to the vacuum \( (\varepsilon_2/\varepsilon_0) \) as free parameters – parameters which are controllable by changing composition of the fluid in which the erythrocytes are suspended. Assuming that rouleaux do form (the condition \( a < a_c \) given above is satisfied) one can plot a phase diagram (see figure 3) in the \( \varepsilon_2 - I \) plane, showing in which regions the rouleaux are stable. For stable rouleaux it is theoretically necessary to have sufficiently small ionic strength and/or sufficiently large values of \( (\varepsilon_2/\varepsilon_0) \). The temperature dependence of the Casimir energy is very weak for the problem at hand, but may be of importance in other systems.

It is important to note that rouleaux formations are usually observed in significantly artificially diluted blood. It is also known that such formations can be unstable in solutions of sufficiently high ionic strength. It would be of great interest for this model to investigate quantitatively the complete phase diagram, especially as quite a number of approximations and idealizations go into figure 3.

We are keenly aware that there are many approximations that have to be made in order to compare any sort of calculation with data. Red blood cells are obviously complex heterogeneous dielectrics with complicated frequency responses, they are certainly not perfect disks, etc. That said, we do feel that the fact that one does not find wild disagreement with simple models and physiological data suggests that further research is of interest. Future work could include:

- the construction and study of model systems with more controllable geometries and dielectric properties (i.e. uniform disks of known dielectric properties and surfaces treated so they carry known charges);
- a more detailed study of the electromagnetic properties of real cells to enable more detailed calculations for real blood to be performed
more careful treatment of deviations from flatness of the red blood cells (see, for example, [11] for work in that direction), including interactions between points of very near approach where the (non-retarded) van der Waals forces might provide a better description of the physics there, and, again, provide a more accurate description of real blood.

5. Implications
In addition to providing an possible explanation for the otherwise mysterious attractive force which compensates the electrostatic repulsion of erythrocytes in rouleaux, this work opens up the possibility of numerous experimental tests, both in blood and in novel colloids with nonspherical particles in suspension. The fact that the Casimir energies involved are significant suggests that studies of colloidal systems may provide novel approaches to studies of the Casimir effect which avoid the extremely difficult techniques employed in past studies[12, 13, 14]. It also suggests that the Casimir effect will be of importance in the burgeoning fields of nanotechnology and nanomedicine as devices approach the size of single cells[15, 16].

We also suggest that since living cells are able to change the local ion concentration nearby via various pumping mechanisms in or out of cell bodies, this offers a means of controlling adhesion or separation of cells from each other or from various boundaries at the cellular level in living organisms. Whether or not this is actually realized in nature is an open question, but an interesting one which might find broad applicability.

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