

# Theoretical model of reticulocyte to erythrocyte shape transformation

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## Abstract

A theoretical model describing the kinetics of reticulocyte shape transformation was developed. The model considers the evolution of a simple cellular shape under transmembrane pressure difference, and proposes a four-parameter axisymmetric approximation of the cell surface. The mathematical analysis considers plasma membrane tension in the plane of bilayer leaflets, membrane spontaneous curvature and transmembrane transport of water. Cytoskeleton dilatational and shear rigidity, and the energetic barrier preventing the decrease of cell volume below a certain minimum are also incorporated. The set of adequate physical assumptions allowed for formulation of the equation for free energy of the investigated system. Computer simulations of cell shape changes, down to the state of free energy minimum, together with estimation of the time needed for the resulting transport of water, revealed a complex, three-phase picture of temporal alterations in cellular geometry with a wide spectrum of final results, and led to propose a standard model of reticulocyte–erythrocyte transformation. According to the model, both cell volume and surface undergo changes, and the work of the pressure, initially accumulated in the cytoskeleton, is consumed for local bending of the cell membrane. Further simulations with modified initial shape or parameters of the standard model show the trajectories of system evolution and help in better understanding the conditions for the erythro-, sphero-, ovalo-, stomato-, and leptoidal metamorphosis of maturing red blood cells. The stability of the final biconcave shape was also verified. Spherogenic modifications were discussed in the context of spherocytosis. Future development of the model was proposed.

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## 1. Introduction

The red blood cell (RBC) membrane consists of 52% protein, 40% lipid and 8% carbohydrate (Freitas, 1999) and is responsible for many of the physiological functions and mechanical properties of the cell. The RBC membrane skeleton is a multi-protein complex formed by structural proteins including predominantly  $\alpha$  and  $\beta$  spectrin, ankyrin, protein 4.1 and actin. The membrane skeleton proteins interact with the lipid bilayer and transmembrane proteins to provide the RBC with strength and plasticity.

There are two types of interaction among the components of red cell membrane skeleton: vertical interactions among the membrane skeleton and the lipid bilayers and

horizontal interactions between components forming the membrane skeleton network of proteins. Disruption of the interactions among components may cause a loss of structural and functional integrity of the membrane (Tse and Lux, 1999). Most of the inherited disorders of red cell membrane proteins produce characteristic morphological changes of the RBC.

Since pathomorphological changes are indicative of numerous diseases (Yawata, 2003), there is little doubt of the importance of elucidating the mechanism governing erythrocyte shape. There are two general hypotheses regarding RBC shape (Nakao, 2002): the lipid bilayer coupled theory (Sheetz and Singer, 1974) and the protein network scaffold theory (Khodadad et al., 1996), recently combined to successfully describe the crenated, echinocytic shapes (Mukhopadhyay et al., 2002) or the stomatocyte–discocyte–echinocyte sequence (Lim et al., 2002). The

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resultant area-difference–elasticity model with spontaneous curvature and the membrane skeleton, ADE–SC–MS (Svetina et al., 1985; Helfrich, 1973; Evans and Skalak, 1980), which considers the membrane as a closed system, can be successfully applied in investigations of locally stable configurations of erythrocyte shape at fixed cell volume and neutral surface area, but at a varying area difference between the bilayer leaflets. The area difference is considered as deviating from its relaxed value, treated as a constant key parameter. This model can also be adapted to establish short-term deformations of erythrocyte under applied external stress (Li et al., 2005). Alternative hypotheses are also under consideration (Gimsa and Ried, 1995).

On the other hand, the changes in area and volume of an animal reticulocyte in vivo, with dynamics of changes reaching three tenths percent per day, are well documented (Waugh et al., 1997). Also in the case of human reticulocyte, clinical practice has shown a decrease in volume from about  $150\ \mu\text{m}^3$  (Dhaliwal et al., 2004) for an orthochromic normoblast, which has extruded its nucleus, to about  $90\ \mu\text{m}^3$  (Karvellas et al., 2004) for a final disc. However, even a circulating mature RBC decreases its volume and area during its life span of 120 days (Mohandas and Groner, 1989). It becomes obvious that during erythropoiesis, especially at the last stages of maturation of RBCs, dramatic changes occur in the structure and organization of the cell (Waugh et al., 2001). Hence, if we want to describe the dynamic process of reticulocyte or erythrocyte aging, the passive picture of elastically deformed cell with conserved volume and area should be changed into an active one.

To “activate” the presented picture of a maturing cell, we proposed to give up the ADE paradigm of a closed system of membrane layers. Instead, we postulate treating the *plasmalemma* as an open system, and suggest the existence of active rearrangement processes establishing and maintaining specific concentrations of particles within the membrane. The candidates for such remodeling processes can be membrane vesiculation (Knowless et al., 1997) and membrane fusion with shed internal vesicles (Hamill and Martinac, 2001). As assumed for protoplasts, such processes can adjust the surface tension (Wolfe et al., 1986).

Adopting and generalizing the above idea, we assumed that during reticulocyte maturation constant surface tension is fully stabilized, but may differ between membrane leaflets. This led to the membrane tension–spontaneous curvature–membrane skeleton model, MT–SC–MS. It was additionally supplemented by temporal analysis of water transport related to change in cytoplasmic volume. Similarly to tension, the pressure difference across the membrane was also considered as constant.

To approximate the cell shape, rotational invariance was assumed, and the set of the two, simplified and sewn together, Evans–Fung-type (Evans and Fung, 1972) functions of the radial distance was applied. The parameters

were: azimuthal and tangential radii at the cell “equator” (the stitch ring), and the distances of the cell “poles” from the “equator” plane, which in general may differ.

A set of the above physical assumptions led to derivation of an equation for the free energy of the investigated system, summing the energies of surface tension, membrane-bending, shear and extensional deformation of the cytoskeleton, and the volumetric work. Additionally, the infinite energetic barrier, preventing the decrease of the cell volume below a certain minimum, was incorporated to mimic non-compressible cellular contents.

Next, a set of computer simulations of cell shape changes leading to the state of the free energy minimum was performed, with simultaneous estimation of the time needed for the accompanying alteration of volume.

During the first round of study, the physical quantities involved were carefully adjusted, yielding the standard model of the dynamics of reticulocyte–erythrocyte transformation, which meets the pre-defined geometrical and temporal requirements. The result shows that even a small pressure difference across the membrane could force a transition in the shape of a cell from a sphere to a biconcave discocyte, as already reported (Tachev et al., 2000). A complex picture of temporal changes in cellular shape, volume, area and energy is also revealed.

Subsequently, the second round of simulations, concerning the role of modifications of initial reticulocyte shape, difference in pressure, membrane surface tension, spontaneous curvature, and cytoskeleton density or rigidity, was performed and discussed in the context of conditions for erythroidal, spheroidal, ovaloidal or stomatoidal transformation of maturing RBC. Erythrocyte spherocytosis was considered as a pathological reference. The biconcave erythrocyte–spherocyte or leptocyte transformation of a modified mature cell was also analysed.

The presented model can be only applied for description of an open membrane system, characterized by relatively slow kinetics of geometric changes. Its possible extension for modeling rapid deformation of a closed extendible *plasmalemma* system was suggested.

## 2. Theoretical approach

A single reticulocyte or erythrocyte cell in a physiological environment was modeled as a mechano-chemical set of two bilayer leaflets, underlaid by a submembrane cytoskeleton network, encapsulating the cytoplasm and surrounded by the external medium (Fig. 1a). To describe the temporal transformation of the cell shape, attention was focused on the imagined surface between the membrane leaflets. For simplicity, it was assumed that such a surface was axisymmetrical, and, in naturally oriented cylindrical coordinates  $r$ ,  $\varphi$ ,  $z$ , its  $\varphi$ -independent geometry could be described by two Evans–Fung-type

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