Mathematical Analysis of Mammary Ducts in Lactating Human Breast

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***Abstract*— This work studies a simple model for milk transport through lactating human breast ducts, and describes mathematically the mass transfer from alveolar sacs through the mammary ducts to the nipple. In this model both the phenomena of diffusion in the sacs and conventional flow in ducts have been considered. The ensuing analysis reveals that there is an optimal range of bifurcation numbers leading to the easiest milk flow based on the minimum flow resistance. This model formulates certain difficult-to-measure values like diameter of the alveolar sacs, and the total length of the milk path as a function of easy-to-measure properties such as milk fluid properties and macroscopic measurements of the breast. Alveolar dimensions from breast tissues of six lactating women are measured and reported in this paper. The theoretically calculated alveoli diameters for optimum milk flow (as a function of bifurcation numbers) show excellent match with our biological data on alveolar dimensions. Also, the mathematical model indicates that for minimum milk flow resistance the glandular tissue must be within a short distance from the base of the nipple, an observation that matches well with the latest anatomical and physiological research.**

I. INTRODUCTION

Evolution of many biological flow systems has given rise to structures that provide better access paths for the flow. Specifically, tree-shaped mass transfer structures are common in biological organs, e.g. the lung, the kidney, the breast, and other vascular tissue. A deeper understanding of this complex branching architecture of organs is essential for elucidating both the physical basis of the transport processes, and the pathology of many human diseases, such as agenesis and asthma in the kidney and lung, as well as breast carcinoma, a disease of terminal ductal lobular units [1]. Many aspects of the diagnosis, healing and investigation of the origin of breast diseases would significantly benefit from a detailed knowledge of the breast branching morphogenesis [2]. A great number of conventional breast conditions such as ductal blockage, breast engorgement, breast abscess, and galactocele can render breastfeeding difficult and sometimes impossible. There are many factors that contribute to diseases of the breast, but among the most important are those that relate to the mechanical properties of the breast, e.g., ductal physical properties. Milk production in the breast (diffusion in sacs), the factors that move the fluid of milk in the ducts toward the nipple (sucking pressure) are all essential mechanical processes. Despite the clear advantage of a fundamental understanding of the branching structure properties in the human breast ductal system, this has not yet been the subject of careful mathematical modeling and evaluation.

The mathematical model proposed in this paper can be utilized to deduce the milk flow from the mechanical properties of the bifurcated ducting structure in the lactating breast. Our model represents the total path from the production zone (alveoli) to the outlet zone (nipple), leading to closed-form expressions that yield the milk flow parameters from the geometric parameters of the model. An immediate example of the applications of this model is the calculation of flow resistance as the ratio of the pressure drop and the milk flow rate. Flow resistance is an important mechanical property of the breast ductal system that must be successfully overcome by the sucking pressure. Calculation of milk-way resistance is made possible by the notion that the ductal tree behaves like a connected conduit through which flows an incompressible fluid (milk). This paper finds a range for the optimum number of branchings based on the easiest milk flow through ducts, in other words the minimum overall flow resistance. It is demonstrated that the combination of convective and diffusive mechanism allows for the maximization of milk transfer through the mammary ducts in order to achieve the best use of this system.

II. THEORETICAL MODELING OF FLOW RESISTANCE

Milk flow in the lactating breast has two paths: diffusion of blood-derived components (protein, glucose and fat) through alveoli (diffusive resistance), and flow through mammary ducts (convective resistance). The total minimum flow resistance is obtained when the structure is arranged in a way that the flows with high resistance (alveoli) occupy the smallest scales of the flow system, while the flows with the lower resistance (ducts) inhabit the larger scales.

A. Mass Diffusion Resistance

During lactation, the infants sucking stimulates the hormone, Oxytocin, and prompted by that, alveoli walls start contracting [3] and the bloodstreams (milk ingredients) approach the capillaries near the breast tissue into alveoli to form the building blocks of milk. The bloodstream moves through the cells that line the alveoli and into the milk. Assuming a steady diffusion of fluid with density, ρ, through the alveolous' wall with thickness of δ, and surface area of A, the rate of the diffusion $\dot{m}$ (temporal rate of arrival of milk mass in the sac) in one dimensional form will be [4]:

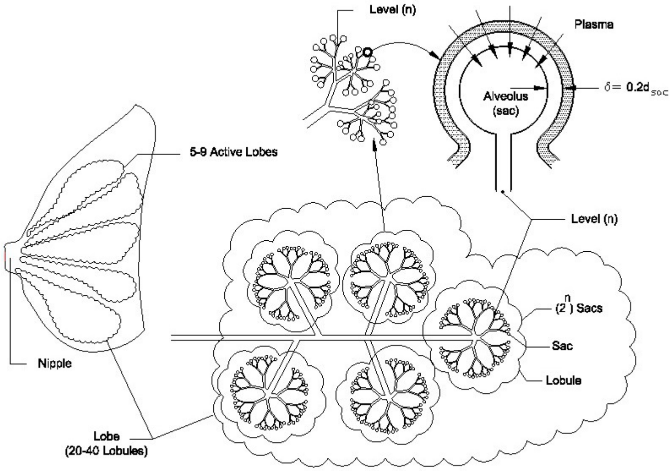

Fig. B.1. The architecture of each lobe, consisting of several lobules

$$\dot{m} = \frac{\rho D_f A}{\delta}\, \Delta M \tag{1}$$

where D_f is the diffusion coefficient (m^2/s) [5] of blood through the membrane walls and ΔM is deriving potential for flow of mass through the wall. Considering the alveoli muscle contraction (ΔP_{pl}), the volume changes of the alveoli by flow of bloodstreams, and the bulk modulus of elasticity (E) of the alveoli tissue, the deriving potential (ΔM) can be calculated as $\Delta P_{pl}/E$ [4].

δ represents the total distance from blood side to the milk side in alveoli (Fig. B.1). δ includes the capillary cell lining, the basement membrane, and the two epithelial layers. The recent studies [7] have shown that the thickness of alveoli is approximately $\delta = 0.2d_{sac}$. Alveolar sacs can have various shapes , but in a more simplistic approach they can be considered mostly spherical with the alveolar diameter set as d_{sac}. Therefore, the total mass of blood components diffusing to the alveolar sacs will be:

$$\dot{m} = \frac{\pi d_{sac}\, \rho\, \Delta P_{pl}\, D_f}{0.2E} \tag{2}$$

Our model consists of 2^n sacs in each lobule, and "a" lobules per lobe (Fig. B.2), therefore the total number of sacs per lobe is $(2^n \times a)$ resulting in a proportional mass flow rate (Equation 3) physiologically this means that each parent duct divides into two identical daughters. According to the latest literature on human breast anatomy, the number of lobules per lobe is estimated to be between 20-40.

Therefore, the total diffusive mass flow rate as a function of pressure drop will be:

$$\sum_{0}^{n} \dot{m}_{sac} = (2^n \times a)\frac{\pi d_{sac}\, \rho\, \Delta P_{pl}\, D_f}{0.2E} \tag{3}$$

and the diffusive resistance will be:

$$R_{df} = \frac{0.2E}{(2^n \times a)\pi d_{sac} \rho D_f} \tag{4}$$

We make one more manipulation to this equation, motivated by the fact that the measurement of d_{sac} is challenging because it requires histoanatomical analysis of human lactating breast tissue, and it may have a functional relationship to other variables in the equation, in particular the bifurcation number n. Therefore:

$$d_{sac} + \sum_{i=0}^{n} L_n = \sum_{i=0}^{\infty} L_n \tag{5}$$

Substitution for L_n in terms of L_0 from Equation (9) and simple calculations yield:

$$d_{sac} = \frac{1}{1-2^{-1/3}} L_0 - \frac{1-2^{-(n+1)/3}}{1-2^{-1/3}} L_{=} \frac{4.85}{2^{(n+1)/3}} L_0 \tag{6}$$

Therefore, the diffusion resistance for one lobule in Equation (4) will be:

$$R_{df} = (\frac{0.0412\ E}{a\ \pi\ L_0\ \rho\ D_f})\ 2^{(\frac{-2n+1}{3})} \tag{7}$$

B. Convective Resistance

Milk flows along a conduit with circular cross-section. Considering the largest values of initial duct diameter (2mm), maximum observed milk flow rate (4.8 g/min) [6], and the minimum measured milk viscosity $(1.66\times10^{-6} m^2/s)$[9], the maximum Reynolds number of the milk flow in the conduits will be around 30 which can be considered as laminar flow. Therefore, the milk flow resistance of each of the two ducts arising from bifurcation n can be represented by the well-known Hagen-Poiseuille equation[10] as:

$$R_d(n) = \frac{128 \mu L_n}{\pi \rho D_n^4} \tag{8}$$

R_d is the resistance of a single duct, ρ, μ, D_n, and L_n stand for milk density, dynamic viscosity, duct diameter, and duct length (in generation n) respectively. This formula often appears in texts of pulmonary physiology [11]. The convective resistance calculation is based on a single suckling pulse. In a separate work, the authors have studied the behavior of milk flow in mammary ducts with pulsating flow during the total period of breastfeeding [8].

For the geometry of the model, a simple structure of the mammary ductal tree has been considered with dichotomous branching scheme for each lobule (Fig. B.2). Each parent duct is divided into two identical daughters and this division is repeated many times, with each successive division being called a *generation*. Assuming complete symmetry, the value of two dimensionless ratios, D_n/D_{n-1} and L_n/L_{n-1} which are the ratio between consecutive duct diameters and duct lengths, can be found by constructal law which has been used in several other natural and biological domains to simplify the theoretical calculations of a complicated branching system [13], [12]:

$$\frac{D_n}{D_{n-1}} = 2^{-1/3} \quad \text{and} \quad \frac{L_n}{L_{n-1}} = 2^{-1/3} \tag{9}$$

D_n and L_n are respectively ductal diameter and length in generation n.

With the above assumption, the number of milk paths in generation n is 2^n and the total convective resistance can be obtained by adding the individual resistances in series or in parallel (Fig. B.2). Assuming the same pressure drop across each of the two daughters in the same generation, the convective resistance to the laminar flow in each single duct in generation 0 to n is:

$$R_d(n) = 2^n R_0 \tag{10}$$

where D_0 and L_0 are the diameter and the length of the first mammary duct respectively. In each generation k we note

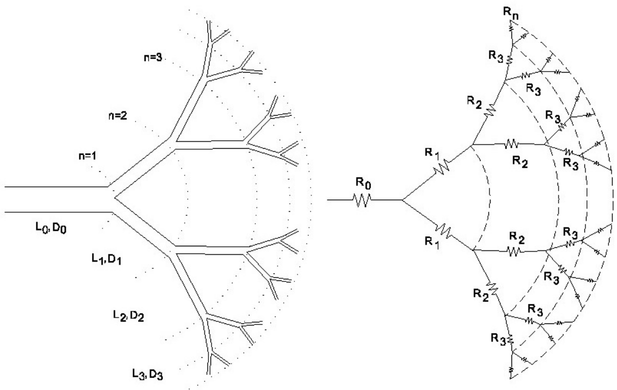

Fig. B.2. Dichotomous branching of ducts and representative model

TABLE I
MILK FLOW RESISTANCE: COMPARISON OF MATHEMATICAL MODELING WITH EXPERIMENTAL DATA FROM THE LITERATURE

No	Sucking Pressure	Mass Production	Ref	Log (R_{tot})
1	60-160(cmH_2O)	$\dot{V}$=28-36(ml/min)	[15]	≈7.2
2	9.5±5.3(cmH_2O)	$\dot{V}$=1.2-8.4(ml/min)	[16]	≈7.0
3	50 ±5.7($mmHg$)	$\dot{m}$=6.6 ± 5.9(g/min)	[17]	≈7.7
4	143±42($mmHg$)	$\dot{m}$=4.6($g/5sec$)	[3]	≈7.3
5	100 ($mmHg$)	$\dot{V}$=5.15×10^{-4}(ml/min)	[18]	≈7.3
6	***Minimum*** possible logarithmic resistance≈6.6 in this study			

that due to symmetry the pressure at the upstream ends of all the ducts in the same generation is equal, and similarly, the pressure at the downstream end of these ducts is also equivalent. Therefore, for computational purposes, one may consider that these ducts operate in parallel. Thus, using the physical laws of combining parallel resistors, the total resistance contributed by generation k is calculated:

$$R_d^{gen}(k) = \frac{R_k}{2^k} = R_0 \tag{11}$$

The generations act in series, therefore the overall resistance increases with the number of generations as follows:

$$R_d^{tot} = \sum_{k=0}^{n} R_d^{gen}(k) = (n+1)R_0 = \frac{128\mu L_0}{\pi\rho D_0^4}(n+1) \tag{12}$$

Bifurcated junctions also add extra resistance to the convective milk flow system. This specific resistance can be calculated by determining the energy dissipation and the pressure drop occurring between the upstream and the downstream of the bifurcated joint. Considering laminar flow in branching geometries following constructal law, Equation (9), the order of bifurcation resistances are small that can be neglected compared to the convective resistance. This has been claimed by Reis et al. [14].

Therefore, the total convection resistance (ductal+bifurcation) for the mammary gland with nipple at $n = 0$ and considering $(n-1)$ bifurcation levels, is given by:

$$R_{cn}^{tot} = (n+1)R_0 \tag{13}$$

III. RESULTS AND DISCUSSION

The convective resistance is an increasing linear function of n. The diffusive resistance is inversely proportional to 2^n. With each increment in n the value of R_{df} decreases by approximately 37%.

A. Optimal Bifurcation Level

For an optimum milk flow in lactating breast, the total resistance which is the summation of the alveolar diffusive resistance in Equation (7) and the convective resistance in Equation (13) is minimized.

As mentioned earlier, 90% of breasts have 15-20 lobes, however only 5-9 lobes in each breast have active mammary ducts that open to the nipple [20]. Since these active ducts are arranged in a parallel configuration, the total resistance in Equation (14) should be divided by a factor of b, with $5 \leq b \leq 9$.

$$R_{tot(cn+df)}^{Breast} = \frac{1}{b}\left[\frac{128\mu L_0}{\pi\rho_m D_0^4}(n+1) + \frac{2^{(-2n+1)/3}E}{24.25a\pi L_0\rho_b D_f}\right] \tag{14}$$

By taking the derivative with respect to n and setting it to zero, it can be verified that the minimum value of the total resistance ($R_{tot\ (cn+ndf)}$) is achieved as:

$$n = 4.9834\ \log\left(\frac{\rho_m\ D_0^4\ E}{a\ \mu\ L_0^2\ \rho_b\ D_f}\right) - 18.5721 \tag{15}$$

The values of ρ_m, ρ_b, D_0, L_0, ν, E, a, b and D_f are listed in [8]. These parameters have been determined experimentally, with appropriate references noted in the table I. These values depend on the details of the individual anatomy, therefore they do not have a fixed value across the population and vary between women [20]. Using the average value of each parameter, Equation (15) leads to the optimum bifurcation level of $n \approx 25$(Fig. C.3)

Recall that the optimization of the bifurcation levels was based on analytical minimization of milk flow resistance. The natural system that is represented by this model is also presumed to be optimized (e.g. by natural selection through generations) but since such a natural optimization is random and may not be mathematically exact, one would expect that our model would yield a value for milk flow resistance that is lower bound on the naturally measured values. Indeed our model, based on the average measured quantities mentioned above, yields an optimal (minimal) milk flow resistance of $\log(R_{tot\ (c+df)}) \approx 6.6$.

To validate our finding, we compared this minimal resistance with the experimental data in the literature. There are several experimental studies measuring the sucking pressure (by infant or breast pump) simultaneously with the milk flow rate during breastfeeding in a healthy breast [16], [17], [18], [19], [3]. The experimentally measured milk flow resistance has been between 7 and 7.7 in log scale (Table I). The separation of the model-induced value of 6.6 and the experimental range 7-7.7 should be judged in light of the variability of experimental data. Furthermore, the range of experimental milk flow resistance, in the manner calculated in the table, only covers the variation among experiments but not the variation within each experiment. In other words, the resistance for each experiment is reported via an averaging of the pressure and mass production in that experiment. Without such intra-experiment averaging, a slightly higher variation in experimental data will be obtained, as well as a slightly lower gap between the model-based minimum and the experimental data. The empirical reason for this averaging is the periodic nature of infant suckling pressure which produces a broad range in the measurement of pressure and flow. One may alternatively report the milk flow resistance measured at the peak as well as the trough of the infant suckling cycle. However, that may produce other methodological issues, therefore this table resorts to averaging in each experiment.

Applying the maximum/minimum of milk properties values and ductal physical parameters [8], results in wide range for 9.2< d_{sac} <270.2 micrometers. To examine how this model-derived range compares with biological data, we measured alveolar diameters in 6 breast tissues of lactating women obtained from the Archive of the School of Anatomy, Physiology and Human Biology, The University of Western Australia. Paraffinized tissues were sectioned and imaged as described in [15]. In each of the 6 tissues, 30 representative alveoli from fuller and emptier adjacent lobules were analyzed. In consistence with the simplification of the presented model of spherical alveoli, complex-shaped alveoli such as the alveolus on the bottom right corner of Fig. C.4(Left), were not analyzed. Therefore, the shape of the analyzed alveoli can be described as spherical or oval. For each alveolus, we measured the large and small diameter in a cross-like format (Fig. C.4(Rigth)).

By considering the average values of milk properties and ductal physical properties, the total theoretical length of the breast duct can be calculated as:

$$L_{tot} = \sum_{0}^{n} L_n \tag{16}$$

$$L_{tot} = L_0 \frac{1-(2^{-1/3})^n}{1-(2^{-1/3})} \approx 38 \tag{17}$$

This conclusion is in agreement with, and is validated by, recent findings based on ultrasound imaging [20] revealing that a large proportion of the glandular tissue appears at 30mm radius from the base of the nipple. Any separation between the theoretical model and the biological measurements may be explained by the fact that the theoretical model assumes all branches of the bifurcation tree are equally deep, i.e., to n levels, while in reality the bifurcation levels in different branches of the duct tree are not always exactly equivalent. Some paths in the actual biological trees are terminated earlier than some others, due to the limitations in the natural amount of space available in the breast for the growth of these trees.

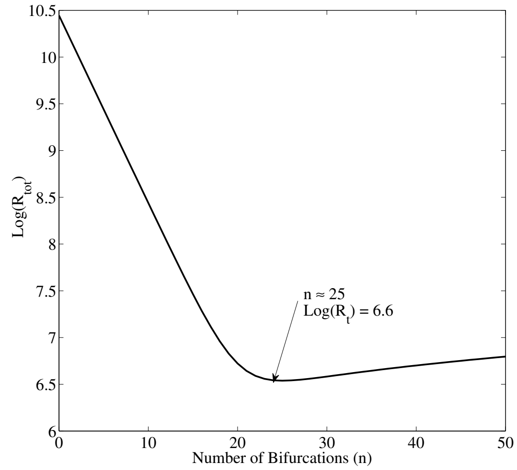

Fig. C.3. Optimum bifurcation level (subject to average parameter value)

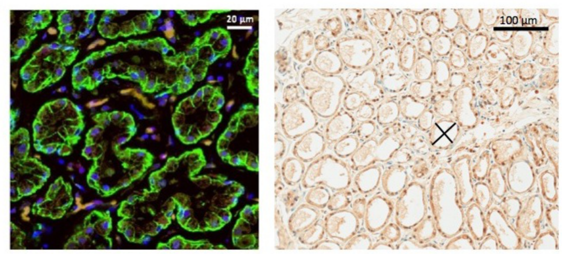

Fig. C.4. A representation of the Alveolar sacs in the human lactating breast [15]. In the immunohistochemistry micrograph on the right, the two black lines indicate how the two alveolar dimensions were measured.

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