

## 2 A model on the dynamics of odontogenic cyst growth

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### Abstract

Odontogenic cysts are non-neoplastic lesions that form as a consequence of the proliferation of epithelial residues that remain embedded in the maxillary bones after formation of dental tissues. The epithelial rests proliferate in response to activating cell mediator signals released during inflammatory processes (for example as a consequence of a tooth infection). In this report we discuss the pathogenesis of odontogenic cysts based on current knowledge and formulate a simple mathematical model of cystic growth. The aim of the modelling is to establish the dynamics (i.e. the long term behaviour) of cyst enlargement based on osmotic pressure differences between the cyst contents and the stomal extracellular fluid. Such osmotic gradient results in water movement into the cyst across the epithelium lining which acts as a semi-permeable membrane. The modelling assumes a (spherical) cyst with a semi-permeable shell of living cells and a core consisting of water and a generic osmotic material (fed by the continuous death of epithelial cells in the shell). The lining cells are assumed to behave like a Maxwell fluid, reflecting the action of physical stresses by the surrounding cyst capsule formed by fibroblasts and collagen fibres. The model couples the cyst radius and the osmotic pressure differences resulting in a system of two nonlinear ordinary differential equations. Using the combination of asymptotic and numerical techniques it is shown that in all parameter regimes the long time behaviour of the cyst is the same and that linear radial expansion is predicted. Moreover, the model predicts that in the early and intermediate stages of cystic growth, osmotic pressure differences play an important role; however, for very large cysts, this role is negligible as cell birth dominates growth.

### 2.1 Introduction

Odontogenic cysts are in general slow growing and pose no major threat to human life. However, since they grow within the maxillary bones, they may cause bone or tooth resorption, bone expansion, fracture or tooth migration. Odontogenic cysts associated with the roots of non-vital teeth are called *radicular cysts*. These arise from the proliferation of the so-called *epithelial rests of Malassez*. Such epithelial rests (small clusters of cells) are the remnants of the *root sheath of Hertwig* which is responsible for the formation of the roots of teeth. The epithelial rests remain dormant during the life of the individual and are located between the root and the jaw bone, in the space occupied by the periodontal ligament. However the rests may proliferate in the presence of an inflammatory process (most commonly due to complications of caries followed by infection of the tooth pulp). *Keratocysts*, on the other hand, comprise about 10% of all diagnosed cysts and are thought to be of developmental origin [3]. This type of cyst grows more rapidly than the radicular cysts and cell division activity is more commonly observed in the epithelial lining. The process of active division of cells, known as *mitosis*, is thought to be more

important in the growth of keratocysts than in radicular cysts. Furthermore, keratocyst exhibit epithelial *budding* (growth into the stromal compartment of the cyst wall) with two consequences: secondary (or satellite) cysts may develop from these localised proliferation foci, and recurrences after surgery are high if the cyst wall is not completely removed. In this report, we present a model of cystic growth dynamics and consider briefly how the model includes both the effects of mitosis and cell lining loss. Then, we describe the implications the model results suggest for cystic growth dynamics. In particular, during the early stages, the cyst growth rate depends on the physical parameters included in the model; however after a sufficiently long time has elapsed, all cysts grow linearly with time. Finally, we suggest some experiments which would test the assumptions of our modelling approach and describe some mechanisms the current model does not include that may alter the conclusions drawn from this study.

## 2.2 Background

Odontogenic cysts form epithelial residues of the tooth-forming organ. While many of these residual epithelial cells remain quiescent throughout life, however, cell mediators and signalling molecules released during an inflammatory process (for example tooth microbial infection as a consequence of dental caries) may trigger the proliferation of the epithelial cell rests.

*Cyst formation.* The epithelial proliferation may reach a critical size at which the diffusion of nutrients within the mass of cells cannot keep pace with the metabolic utilisation of the nutrients (epithelial tissue is not vascularised and nutrients reach all cells by diffusion from the vascular stroma). The lack of nutrients results in degeneration and death of the central cells in the proliferating mass with subsequent liquefaction, creating a new cavity in the epithelial mass. However cells closer to the stroma remain vital.

*Cyst growth.* The degradation of the central cells in the cyst results in an increased osmotic pressure in comparison to the osmotic pressure on the stroma surrounding the cyst. This gradient is believed to draw a water flow into the cavity (to balance the osmotic pressure), inducing an increase in hydrostatic pressure inside the cyst in comparison to the stroma. This volume expansion stretches the epithelial layer and peripheral cells divide further to maintain the epithelial lining intact. Since the epithelial lining regenerates, the osmotic pressure difference will be maintained through the constant shedding of cells into the lumen. At the same time, the stroma reorganises around the cyst wall and produces a capsule relatively rich in collagen fibres.

### 2.2.1 Clinical data

Experimental data regarding cysts is hard to come by since investigation without treatment provision raises a number of ethical issues. Cystic growth is slow, with a radial expansion of only a few millimetres a year [2]. The mitotic rate is small in radicular cysts, meaning that, only a small proportion of living cells are undergoing mitosis at any one time. There have been a few studies aimed at comparing the osmolality, the molar quantity of “osmotically active” molecules per litre, between cyst fluid and serum (i.e. normal tissue fluid). The study of Toller (1970, [1]) showed that in most of the cases tested the osmolality is higher in cyst fluid (mean 0.291 Osml  $\equiv$  0.291 mol) than in serum (mean 0.280 Osml); these values being consistent across several types of cyst.

The osmotic pressure difference  $\Delta P_o$  relates to the difference in osmolality, in this case 0.011OsmL, via the formula

$$\Delta P_o = \Delta M RT,$$

where  $\Delta M$  is the molar concentration difference of “osmotically active” molecules,  $R$  is the ideal gas constant and  $T$  is the absolute temperature. Using  $\Delta M = 0.011\text{mol/m}^3$ ,  $T = 310\text{K}$  and  $R = 8.31\text{J/mol.K}$  the osmotic pressure is, in this case, approximately  $P_o = 28.3 \text{ N/m}^2$ . As will be evident in the modelling to come, the osmotic pressure will change as the cyst develops.

### 2.3 Mathematical model

Given that the timescale of cystic growth of the order of years, water is drawn inside the cavity almost instantaneously, so that the hydrostatic pressure difference, between the cavity and the environment, balances the osmotic pressure difference between the same two media,

$$P_h^+ - P_h^- = P_o^+ - P_o^-,$$

where  $P_h^+$  and  $P_o^+$  are the hydrostatic and osmotic pressures, respectively, in the cavity, while  $P_h^-$  and  $P_o^-$  are the hydrostatic and osmotic pressures, respectively, in the surroundings.

Also, the supply of nutrients remains sufficient to maintain the epithelial cells alive due to the living cells being in contact, or close to, the medium containing the nutrients (such as the local vasculature). Moreover, we assume that the cell lining is a semi-permeable membrane, which allows the passage of water and of nutrients to the cavity; but the degraded material driving the osmosis does not cross the epithelial layer. Therefore, if  $s$  is the total amount of degraded material inside the cyst, then the rate of change of  $s$  is proportional to the surface area of the covering epithelium. So, if  $R$  is the cyst radius, then

$$\frac{ds}{dt} = 4\pi\beta R^2.$$

The parameter  $\beta$ , a supply rate of degraded material into the cavity, will change according to the type of cyst: the value of  $\beta$  will be smaller in a cyst which is losing its cell lining slower than in a “normal” radicular cyst – growing as a response to environmental signals only, and larger for keratocysts in which the epithelial cells actively divide.

We assume, further, that the concentration of degraded cells is uniform inside the cyst. If we consider that each epithelial cell contains the same amount of osmotically active substance, the osmotic pressure becomes proportional to a concentration of degraded material. Also, the concentration outside the cell is assumed constant. This implies that the osmotic pressure in the surroundings is constant as well, and that the jump in osmotic pressures across the epithelial lining is proportional to the difference in concentration of degraded cells, that is,

$$P_o^+ - P_o^- = \alpha (C - C_0),$$

where  $C$  the concentration of material inside the cyst, that is,  $C = \frac{s}{4\pi R^3/3}$ , and  $C_0$  the concentration outside it, assumed constant;  $\alpha$  is the proportionality constant.

It is worth noting that most cysts are roughly spherically shaped, independently on the material that surrounds them. This could be due to the fact that their growth rate

is very low, so when they grow into a bony material, the bone is resorbed and the cyst grows as if there was no obstacle stopping it from expanding. Thus, the stresses on the cyst, seem to have little angular dependence.

Now, the hydrostatic pressure jump balances the stresses in the semi-permeable membrane, and the stresses on the cyst from the surrounding,

$$P_h^+ - P_h^- = f(R, \dot{R}) + f_b(R, \dot{R}),$$

where  $f$ , the physical stresses, is in general, a function of  $R$  and the time derivative of  $R$ ; and  $f_b$  corresponds to stresses due to biological processes.

However, it is not clear which biological or physical stresses should be included. For instance, the fact that in some cases the cells actively divide may affect the stresses the surrounding material exerts on the cyst: it is not clear whether these stresses are important, or whether they are proportional to the rate of change of  $R$ , or proportional to the rate of change of the surface area of the cyst. So, in this work we only will consider the physical stresses of the surrounding material. Also, the equations above allow us to find a single equation relating the radius of the cyst and the stress function, of the form

$$\frac{1}{\alpha}\dot{R}f + \frac{R}{3\alpha}\dot{f} + C_0\dot{R} = \beta. \quad (2.1)$$

Even with this simplification, we still lack information on the properties of this material. All we know is that it is a mixture of fluid, collagenous capsule, and crystalline structures. Thus, we will assume that the material may be modelled as a Maxwell fluid, so the stresses satisfy

$$\tau\dot{f} + f = \mu\frac{\dot{R}}{R}, \quad (2.2)$$

where  $\tau$  is the relaxation time, and  $\mu$  the viscosity of the external medium.

Considering the scalings  $R = R_0\hat{R}$ ,  $f = \frac{\mu}{T}\hat{f}$ ,  $t = T\hat{t}$ ,  $\tau = T\hat{\tau}$ , assuming that  $T = \frac{C_0R_0}{\beta}$ , and defining  $C_B = \frac{\mu\beta}{\alpha R_0 C_0^2}$ , equations (2.1) and (2.2) become

$$C_B\dot{R}f + \frac{C_B}{3}R\dot{f} + \dot{R} = 1, \quad (2.3)$$

and

$$\tau\dot{f} + f = \frac{\dot{R}}{R}, \quad (2.4)$$

with initial conditions  $R(0) = 1$ , and  $f(0) = f_0$ . In equations (2.3) and (2.4), we have dropped all the hats for the sake of simplicity. It is worth remarking that, using the osmotic pressure equation, the material concentration in the core  $C$  is related to the dimensionless function  $f$  via  $C = C_0(1 + C_B f)$ . The solution of these two coupled ordinary differential equations may be found analytically in limiting cases of the parameters  $C_B$ ,  $\tau$  and  $f_0$ , for which some terms in those equations dominate. However, the general solution can be found numerically only.

### 2.3.1 Asymptotic analysis

The coupled nonlinear system of ordinary differential equations (2.1) and (2.2) are not solvable in closed form and in order to understand the model predictions for the evolution

of  $R$  and  $f$  we resort to asymptotic methods. Of particular interest is the determination of timescales for the shifting of importance of the main mechanisms involved in cystic growth. There are three parameters in the model, namely  $C_b, \tau$  and  $f_0$ , for which there is insufficient data to determine their values. Hence, we seek solutions in the six cases in which one parameter is set to be large and small, whilst the other two are of  $O(1)$  size. It turns out that in all cases the (very) large time attractor for equations (2.1) and (2.2) is given by the system

$$\dot{R} \sim 1, \quad f \sim \frac{\dot{R}}{R} \sim \frac{1}{R}, \quad (2.5)$$

implying that  $R \sim t$  and  $f \sim 1/t$  as  $t \rightarrow \infty$ . The model therefore predicts in large time that the radial expansion of the cyst will be linear and the concentration of the internal osmotic material will equilibrate with the external concentration. Hence cystic growth will eventually be governed by cell birth. We also note that in large time the outer fibrous capsule layer behaves like a viscous material with negligible elastic properties.

The details of the analysis are omitted for brevity and summarised in Table 1 (at the end of the report). The Table shows for each limit the appropriate rescalings on time for each of the important timescales (column 2), the rescalings on  $R$  and  $f$  for each timescale (columns 3 and 4) and the “large” time behaviour of  $R$  and  $f$  for each timescale (columns 5 and 6). We note the last line for each limit in the table indicates the timescale and appropriate rescalings for the large time system (2.5) to become dominant. For example, in the case of large  $C_B$ , i.e.  $C_B \rightarrow \infty$ , we expect the behaviour given by (2.5) to dominate in a timescale of  $t = O(C_B)$ , likewise for the large  $\tau$  limit, we expect (2.5) to result in a timescale of  $t = O(\tau \ln(\tau))$ . Below is a short discussion of the salient features drawn out by the analysis for each case.

**Large  $C_B$**  The dimensionless parameter  $C_B$  consist of a number of parameters so there are a number of combinations of relative sizes that can generate a “big”  $C_B$ . However, the value of  $C_B$  will increase if the material supply rate  $\beta$  and fibrous capsule “viscosity”  $\mu$  are *increased* or the initial cyst diameter  $R_0$ , external material concentration  $C_0$  (thereby enhancing osmotic pressure) and osmotic pressure constant  $\alpha$  are *decreased*. There are three main timescales. Growth in the first timescale is dominated by the osmotic pressure difference and the resulting absorption of water forces expansion; the *amount* of new material added to the core by cell death is negligible. There follows two longer timescales in which cell death now contributes to the amount of material in the core and the elastic properties of the capsule collagen fibres become negligible. Eventually, the balance given by (2.5) is reached in an  $O(C_B)$  timescale.

**Small  $C_B$**  As with the large  $C_B$  case, small  $C_B$  may result in a number of ways and its value will decrease by reversing the parameter relationships described in the large  $C_B$  case. This case effectively implies that the osmotic pressure difference has negligible effect on growth and cell birth dominates growth. As a result, the large time scenario (2.5) occurs in  $O(1)$  time.

**Large  $\tau$**  This case implies that the fibrous capsule responds to the growing cyst, at least in the short term, like an elastic layer (the viscous properties being negligible). There are a number of timescales in this case, although the latter ones are technical

rather than have any biological significance. Initially, the osmotic pressure remains constant, the material concentration in the core being held stable due to amount of new material introduced by cell death is exactly compensated by the influx of water; consequently linear growth is predicted. Eventually a second, longer timescale ensues in which the viscous properties of the fibrous capsule come into play; this has the effect of “taking the slack” with influx of water, hence the internal material becomes diluted and the osmotic pressure decreases exponentially. The large time of linear radial expansion evolves in this timescale, i.e.  $t = O(\tau)$ . There follow two minor timescales of little interest before evolving to the balance given by (2.5).

**Small  $\tau$**  The case of  $\tau \rightarrow 0$  effectively assumes that the fibrous capsule behaves as a viscous material, i.e. it readily responds to cystic growth by taking the slack rather than by stretching. Water influx by the osmotic pressure difference contributes initially to cystic growth, however, the balance given by (2.5) dominates as equilibration of material concentration occurs in  $O(1)$  time.

**Large  $f_0$**  Large initial hydrostatic/osmotic pressure may arise, for example, if there is a very high concentration of material in the core of the cyst compared to surrounding tissue. Growth initially starts very rapidly due to a massive influx of water to balance the osmotic pressure difference. There follows two long timescales in which there is apparently negligible cystic growth and the osmotic pressure seems to settle to some fixed, non-zero level. However, there *is* a small amount of cystic growth and in large time,  $t = O(f_0^{1/3})$ , we get the balance given by (2.5).

**Small  $f_0$**  Here we assume that initially there is a negligible hydrostatic/osmotic pressure across the cystic epithelial lining, which may arise, for example, when the concentration of material inside and outside the cyst are nearly equal. There are two phases of interest. Initially, there is a rapid increase in osmotic pressure due to the water influx being too slow to compensate for the additional material being added to the core by cell death; in time, this material concentration will build up sufficiently for the osmotic pressure difference to become non-negligible. Consequently, a full balance, i.e. (2.1) and (2.2), results in  $O(1)$  time and soon the balance given by (2.5) ensues. The very small initial timescale suggests that this case is unlikely to be observed.

There are of course a number of combinations of these limits that could be considered. The more interesting cases arise when the parameters are large, for example  $1 \ll C_B = O(\tau)$  and  $1 \ll C_B = O(\tau^{5/3})$  seem to be distinguished limits. However, these cases offer no further insights and will not be discussed further.

### 2.3.2 Numerical results

Figures 8 and 9 show log-log plots of the evolution of  $R$  and  $f$  for  $C_B = \tau = f_0 = 1$ . The dashed lines are the large time solutions given by (2.5) and in both cases these solutions agree well (although not exactly) with the full solutions from about  $t = 1$ . It can be shown that the approach to these large time solutions is given by

$$R \sim t - \frac{2C_B}{3} \ln(t), \quad f \sim \frac{1}{t} + \frac{2C_B \ln(t)}{3t^2},$$

as  $t \rightarrow \infty$ , explaining the apparent slowness in convergence of the curves. Figures 10 and 11 show two examples of the asymptotic approximations compared to the numerical solutions. In both cases good agreement is obtained between the numerical solution (solid curves) and the asymptotic solutions (various dotted and dashed curves) in the appropriate timescales. We note that it is the asymptotic solutions shown in the figure are the full, leading order asymptotic solutions for each timescale, rather than the “large time” expansions given in the last two columns of Table 1.

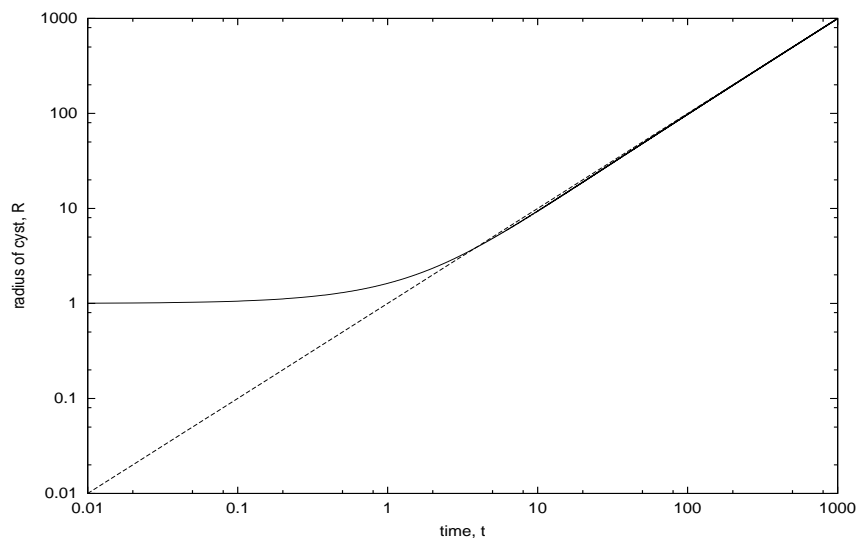


Figure 8: Log-log plot showing the evolution of the cyst radius, with  $C_B = \tau = f_0 = 1$ .

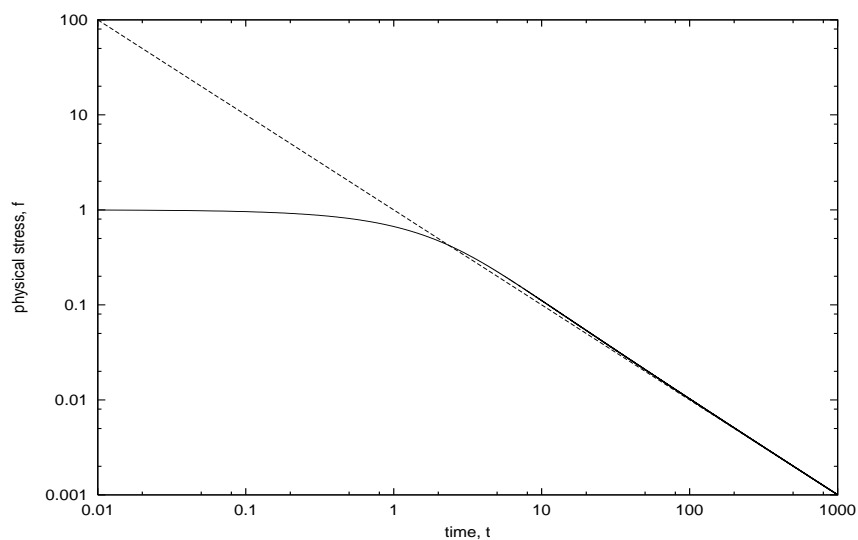


Figure 9: Log-log plot showing the evolution of the osmotic pressure, with  $C_B = \tau = f_0 = 1$ .

## 2.4 Conclusions

In this report we present a simple mathematical model to describe cystic growth, based on cell birth (and death) and osmotic-hydrostatic pressure balances. We assumed that the

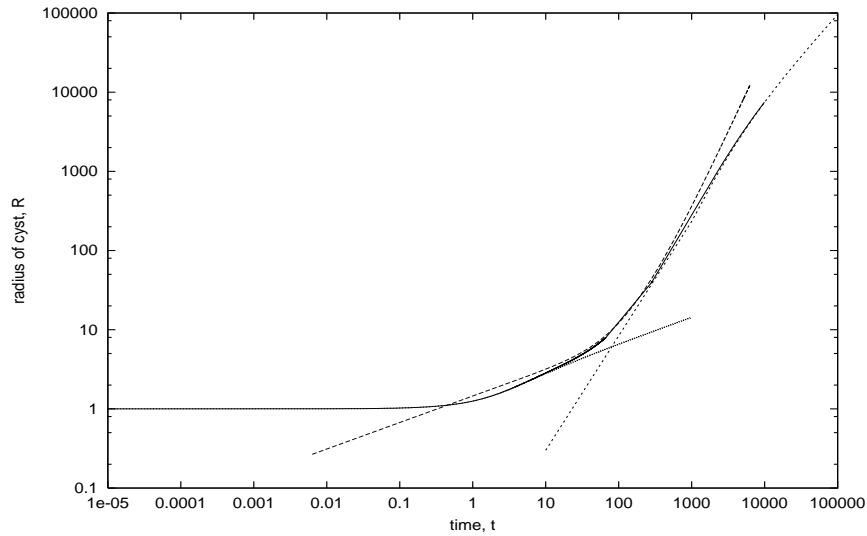


Figure 10: Log-log plot showing the evolution of the cyst radius, with  $C_B = 1000$ ,  $\tau = f_0 = 1$ . The solid curve is the numerical solution of (2.1) and (2.2) and the dotted and dashed curves are the asymptotic approximations.

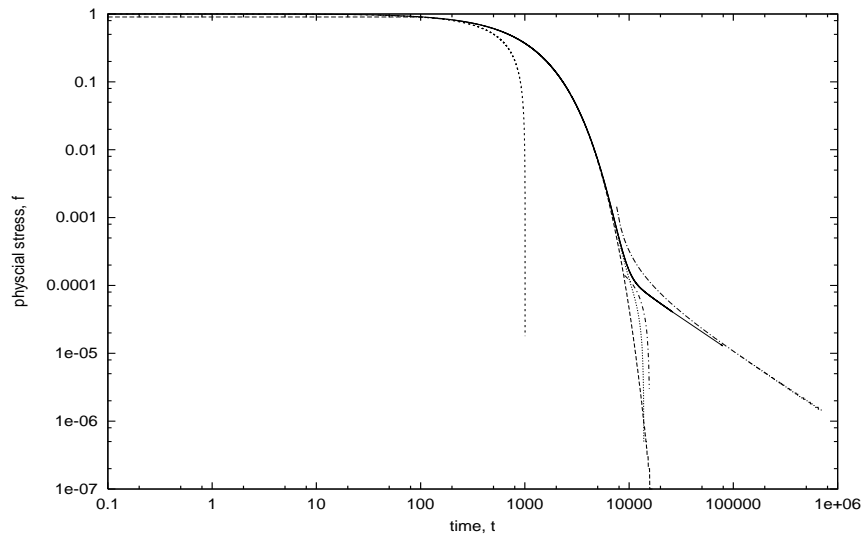


Figure 11: Log-log plot showing the evolution of the osmotic pressure difference, with  $\tau = 1000$ ,  $C_B = f_0 = 1$ . The solid curve is the numerical solution of (2.1) and (2.2) and the assorted dotted and dashed curves are the asymptotic approximations.

cyst consists of a thin shell of living cells, behaving as a Maxwell fluid (reflecting action of a fibrous capsule), surrounding a fluid core. Material feeding into the core by cell death leads to osmotic pressure differences between the cyst core and its surroundings, which, together with cell birth, drives cystic growth. The dimensionless version of the model consists of 3 parameters, namely  $C_B$ ,  $\tau$  and  $f_0$ , the values of which cannot be determined accurately from existing data. Nevertheless, the asymptotic and numerical solutions described in Sections 3.3 and 3.4 demonstrate that, regardless of the parameters, the cysts radius will eventually grow linearly with the osmotic pressure differences decaying



to zero. In dimensional terms the long time behaviour is given by

$$R \sim \frac{\beta}{C_0}t, \quad f \sim \frac{\mu}{t}, \quad (2.6)$$

recalling that  $\beta$  is the supply rate of degraded material,  $C_0$  is the external concentration of the osmotic material and  $\mu$  is the viscosity of the external material. We note that the manner and timescales in which this behaviour occurs is very much dependent on the parameter values.

Cysts when diagnosed and treated can be up to a few centimeters in diameter; in the context of the model, this would probably represent cysts at a fairly mature stage of development. However, these cysts still have measurable osmotic pressure differences, which suggests that the large time growth pattern, given by 2.6, has yet to be achieved. This has two possible implications. Firstly, at least one of the dimensionless  $C_B, \tau$  and  $f_0$  is large, otherwise negligible osmotic pressure differences would be expected. Secondly, radial growth may not be linear at the time of diagnosis. Nevertheless, despite the model indicating that, in the long term, osmotic pressure differences do not influence growth, it does suggest that it plays an important role in the early and intermediate stages of cyst development. From this we can conclude that when a cyst is diagnosed, the osmotic pressure differences are still an important factor.

The model should be applicable for any kind of cyst if an osmotic pressure drop is driving the growing process, but only if the growth rate is very slow. For the particular application which led to this study, we predict that dental cysts will grow indefinitely, unless we include other physical or biological processes that may affect cystic growth. For instance, here the supply rate  $\beta$  implicitly includes any mitosis or lining loss effects; however, basal cells on a Keratocyst surface are four times more densely packed than the cells lining a radicular cyst, and thus it is not clear whether mitotic cells will be the source of important stresses on a Keratocyst surface. These stresses probably ought to be included in the force balance equation as *biological* stresses, such as a mitotic stress function (proportional to the rate of change of either, the cyst radius,  $f_m \propto \dot{R}$ , or the cyst surface area, that is  $f_m \propto R\dot{R}$ ), a cell lining loss stress function, and so on.

Also, physical stresses, of the surroundings on the cyst, clearly will be smaller if the cyst is growing in soft tissues rather than in bone, unless the process is slow enough for the bone to be resorbed by the body at a similar (or larger) rate than that of the cyst growth, so that the cyst is not deformed from its spherical shape. If this were not true, the stresses would have spatial dependence on the angular direction, and the cyst would not be spherically shaped; in that case, the model would have to be modified accordingly. However, experimental observations support our assumptions in this respect.

Finally, it is difficult to assess whether the concentration of material inside the cyst is uniform or not, and it would be important to carry out experiments to test this hypothesis, and to improve the model. It may be necessary, as well, to divide the material inside the cavity into more subunits so as to consider biological-chemical processes particular to certain species in more detail. For instance, both the osmotically active substance, and the water drawn into the cavity, are fundamental in this problem and may be separated from the rest of the cavity contents. In fact, if the osmotically active substance could diffuse out of the epithelial layer, the flux of water into the cell would decrease, and so would the growth rate of the cyst; this proposed mechanism could even stop the growing process completely. Also, the role in cystic growth of other substances in the cavity, such

as albumin, or cholesterol crystals, should be defined more clearly in future experiments and models.

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limit	scalings			$t^{(i)} \rightarrow \infty$ behaviour	
	$t =$	$R =$	$f =$	$R^{(i)} \sim$	$f^{(i)} \sim$
$C_B \rightarrow \infty$	$t^{(1)}$	$R^{(1)}$	$f^{(1)}$	$(3f_0)^{1/3} t^{(1)1/3}$	$1/3t^{(1)}$
	$C_B^{3/5} t^{(2)}$	$C_B^{1/5} R^{(2)}$	$C_B^{-3/5} f^{(2)}$	$\frac{3}{10} t^{(2)2}$	$2/t^{(2)}$
	$C_B t^{(3)}$	$C_B R^{(3)}$	$C_B^{-1} f^{(3)}$	$t^{(3)}$	$1/t^{(3)}$
$C_B \rightarrow 0$	$t^{(1)}$	$R^{(1)}$	$f^{(1)}$	$t^{(1)}$	$1/t^{(1)}$
$\tau \rightarrow \infty$	$t^{(1)}$	$R^{(1)}$	$f^{(1)}$	$t^{(1)}/(1 + f_0 C_B)$	$f_0 - f_0 t^{(1)}/\tau$
	$\tau t^{(2)}$	$\tau R^{(2)}$	$f^{(2)}$	$t^{(2)}$	$f_0 e^{-t^{(2)}}$
	$\tau(\ln(\tau) + \ln(\ln(\tau)) + t^{(3)})$	$\tau(\ln(\tau) + \ln(\ln(\tau)) + R^{(3)})$	$f^{(3)}/\tau \ln(\tau)$	$t^{(3)}$	$1 - \frac{\ln(\ln(\tau))}{\ln(\tau)} - t^{(3)}/\ln(\tau)$
	$\tau(\ln(\tau) + \ln(\ln(\tau))(1 + t^{(4)}))$	$\tau(\ln(\tau) + \ln(\ln(\tau))(1 + R^{(4)}))$	$f^{(4)}/\tau \ln(\tau)$	$t^{(4)}$	$1 - \frac{\ln(\ln(\tau))}{\ln(\tau)} t^{(4)}$
	$\tau \ln(\tau)(1 + t^{(5)})$	$\tau \ln(\tau)(1 + R^{(5)})$	$f^{(5)}/\tau \ln(\tau)$	$t^{(5)}$	$1/t^{(5)}$
$\tau \rightarrow 0$	$t^{(1)}$	$R^{(1)}$	$f^{(1)}$	$t^{(1)}$	$1/t^{(1)}$
$f_0 = 1/\varepsilon \rightarrow \infty$	$t^{(1)}$	$R^{(1)}$	$\varepsilon^{-1} f^{(1)}$	$e^{t^{(1)}/3\tau}$	$e^{-t^{(1)}/\tau}$
	$\tau \ln(1/\varepsilon) + t^{(2)}$	$\varepsilon^{-1/3} R^{(2)}$	$f^{(2)}$	$C_B^{1/3} \left(1 - \frac{C_B^{Z\tau}}{3} e^{-Zt^{(2)}}\right)$	$C_B^{-ZC_B/3} e^{-Zt^{(2)}}$
	$\frac{12\tau + C_B}{9} \ln(1/\varepsilon) + t^{(3)}$	$\varepsilon^{-1/3} R^{(3)}$	$\varepsilon^{1/3} f^{(3)}$	$C_B^{1/3} + \varepsilon^{1/3} t^{(3)}$	$C_B^{-1/3} + C_B^{-ZC_B/3} e^{-Zt^{(2)}}$
	$\frac{12\tau + C_B}{9} \ln(1/\varepsilon) + \varepsilon^{-1/3} t^{(4)}$	$\varepsilon^{-1/3} R^{(4)}$	$\varepsilon^{1/3} f^{(4)}$	$t^{(4)}$	$1/t^{(4)}$
$f_0 = \varepsilon \rightarrow 0$	$\varepsilon t^{(1)}$	$R^{(1)}$	$\varepsilon f^{(1)}$	$1 + \varepsilon Z t^{(1)}$	$1 + Z t^{(1)}$
	$t^{(2)}$	$R^{(2)}$	$f^{(2)}$	$t^{(2)}$	$1/t^{(2)}$

Table 1: Summary of the asymptotic analysis on equations (2.1) and (2.2) in the limits shown in the first column (the other parameters being  $O(1)$ ). The Table shows for each limit the appropriate rescalings on  $t, R$  and  $f$  for the various timescales and the large time behaviour of  $R$  and  $f$  in their respective timescale. Where the leading order solutions are constant, the correction term(s) is(are) also given. The constant  $Z$  is given by  $Z = 3/(3\tau + C_B)$ .