Report on a problem studied at the UK Mathematics in Medicine Study Group Strathclyde 2004
< http://www.maths-in-medicine.org/uk/2004/kidney-function/ >

Modelling the Loss of Kidney Function

Introduction

The kidneys consist of approximately one million filtering units called nephrons; each nephron has a glomerulus where the majority of urine filtration from the blood occurs. Kidney function is assessed by measuring the glomerular filtration rate (GFR, typically 100–150 ml per min) which is the total amount of fluid filtered through these units. When kidneys become diseased some of these glomeruli die. Since there is no mechanism for replacement or regeneration of glomeruli, other glomeruli are required to increase the amount of fluid they filter to maintain the body's required GFR.

It is thought that this increased filtration rate causes damage to the remaining glomeruli, which leads to the death of more glomeruli, and further increases in the required average filtration rate for each surviving glomerulus. If this is the case, then eventually a threshold will be reached where the remaining glomeruli cannot filter enough fluid to maintain the GFR and so the GFR will then decrease also.

Existing theory states that GFR is lost at a rate which declines linearly in time as illustrated in the left hand graph of Figure 1. However, a more recent analysis of data suggests that rate of loss is larger for lower values of GFR, as shown in the right-hand graph of Figure 1.

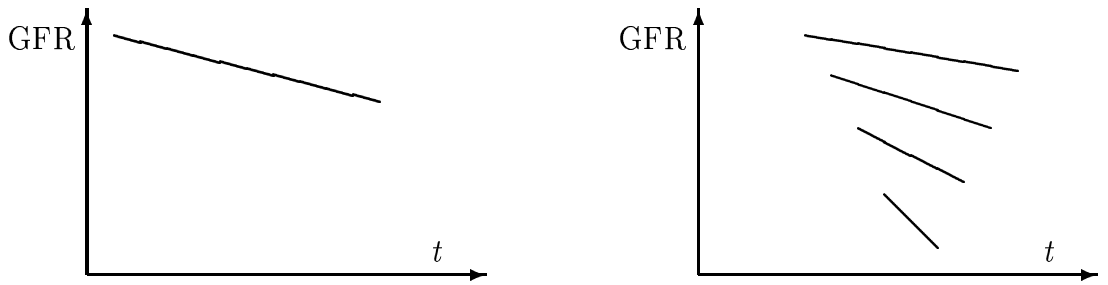

Figure 1: Left: existing theory suggests loss of GFR is linear in time.
Right: recent analysis suggests loss rate is more severe at lower GFR.

Combining the curves from the right-hand portion of figure 1 suggests that the longer-term evolution of kidney function has the form displayed in Figure 2.

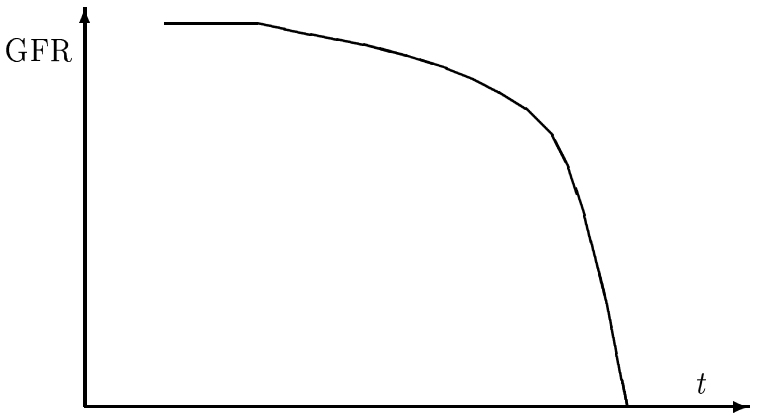

Figure 2: Overall qualitative picture of loss of kidney function over a long timescale.

Until now, a mathematical model of the attrition of glomeruli has been lacking, yet such a model would help test the assumptions underlying the proposed theory.

Knowledge of how the GFR decays would be beneficial in understanding the progress of a variety of diseases all of which have similar effects on the number of active glomeruli.

There are various tests that can be carried out on any theory; for example, removal of a kidney does not lead to a deterioration in the GFR.

Notation

We use the following notation throughout the report:

G_H = total GFR (glomerular filtration rate) for a healthy individual
$G(t)$ = total glomerular filtration rate for an individual, this may vary over time
$N(t)$ = total number of functioning glomeruli

1 Simple models

1.1 Model 1a

In the simplest model we assume that there is a large population of functioning nephrons, and we denote their number by $N(t)$. Thus we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\alpha N, \tag{1.1}$$

where the death rate α depends upon the stress imposed on the kidney as a whole. If there is ample spare processing capacity in the kidney, then we assume the death rate is zero, however, if the required filtration rate for each glomerulus is above some critical value r_c, then we assume that the death rate is proportional to the excess of the required filtration rate for each glomerulus above this critical value. Denoting the death rate by

$$\alpha = \alpha_0 \left(\frac{G_H}{N} - r_c \right)_+, \tag{1.2}$$

where

$$(X)_+ = \begin{cases} X & X > 0 \\ 0 & X \leq 0, \end{cases} \tag{1.3}$$

we have $\dot{N} = 0$ if $N \geq G_H/r_c$ and

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\alpha_0 (G_H - r_c N), \tag{1.4}$$

if $N < G_H/r_c$. Given the initial data of $N(0) = N_0 < G_H/r_c$, this is solved by

$$N(t) = \frac{G_H}{r_c} - \left(\frac{G_H}{r_c} - N_0 \right) e^{\alpha_0 r_c t}. \tag{1.5}$$

The catastrophic loss of kidney function occurs as $t \nearrow t_c$ where $N(t) \to 0$, this implies

$$t_c = -\frac{1}{\alpha_0 r_c} \log \left(1 - \frac{r_c N_0}{G_H} \right). \tag{1.6}$$

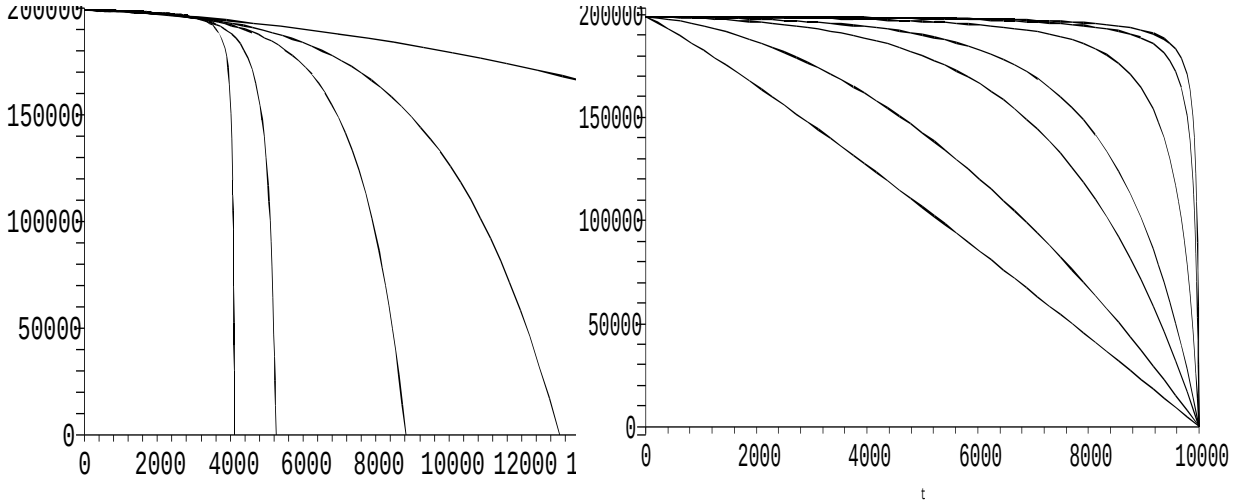

Figure 3: Illustration of possible solutions for (1.8), $N(t)$ is plotted against t, N is measured in absolute numbers of functioning nephrons, and G_H/r_c is chosen so that loss occurs whenever N is below 200000.

On the left, time has been scaled so that $\alpha_0 = 1$, and a range of $p = q = 0.5$, 0.9, 1.1, 1.5, 1.9 are shown. Smaller values of q result in later extinction times.

On the right, α is scaled so that extinction occurs at $t = 10^4$, and a range of $p = q = 0.1$, 0.5, 0.9, 1.1, 1.5, 1.9, 2.1 is shown, these correspond to $\alpha_0 = 13.902$, 3.717, 1.304, 0.8816, 0.5257, 0.4111 and 0.3886 respectively.

Other parameters are $G_H = 100$, $r_c = 1/2000$. In both cases, larger values of q show a more severe final decay in N (vertical axis). Model 1a corresponds to $p = q = 1$, and so lies between the displayed cases of 0.9 and 1.1.

1.2 Model 1b: a nonlinear model

A wider variety of behaviours at the point of catastrophic loss of glomeruli can be explained by changing the linear behaviour in (1.1) and (1.2) to power-law. In general we can rewrite these as

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\alpha_0 N^p \left(\frac{G_H}{N} - r_c\right)_+^q; \tag{1.7}$$

in the special case $p = q$, explicit analytic solutions are available.

$$N(t) = \frac{G_H}{r_c} - \frac{(G_H - r_c N_0)}{r_c}\left[1 + \frac{\alpha_0 r_c (1-p) t}{(G_H - r_c N_0)^{1-p}}\right]^{1/(1-p)}. \tag{1.8}$$

These are illustrated in Figure 3. The time at which $N = 0$ is given by $t = t_c$, hence

$$t_c = \frac{(G_H - r_c N_0)^{1-q} - G_H^{1-q}}{\alpha_0 r_c (q-1)}. \tag{1.9}$$

An alternative scaling time is used in the right-hand part of Figure 3 which shows more clearly the different shapes which can be modelled by varying p.

1.3 Model 1c

As with the other models described above we assume some death rate equation for the glomeruli of the form

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -k(F)N, \tag{1.10}$$

where F is the average flow rate through each glomerulus. We assume that the flow rate can rise to accommodate a loss in the number of functioning nephrons, but is subject to a maximum of F_m. Thus ideally we have $NF =$ a constant (given by $F_0 N_c$) but if this required flow rate rises above F_m, then we assume that glomeruli will actually only process fluid at the rate F_m. Thus

$$F = \min\left\{\frac{F_0 N_c}{N}, F_m\right\}. \tag{1.11}$$

The loss of nephrons will occur at a rate which depends upon the amount by which the flow rate F exceeds some (other) critical flow rate F_c (note we are not necessarily assuming $F_c = F_m$). Thus we have the relationship

$$k(F) = k_0(F - F_c)_+ = \begin{cases} 0 & F \le F_c \\ k_0(F - F_c) & F > F_c. \end{cases} \tag{1.12}$$

Note that if the maximum possible flow rate $F_m < F_c$ (the critical flow rate where damage is sustained) then $F < F_c$ for all time, and no damage can possibly sustained (equation (1.10) implies $\dot{N} = 0$ and there is never any loss of glomeruli). We shall assume that $F_m \ge F_c$, that is the flow rate can exceed the critical rate where damage is caused.

In the first phase of the process, $F_m < F < F_c$ and so $F = F_0 N_c / N$ giving

$$N(t) = \frac{F_0 N_c}{F_c} - \left(\frac{F_0 N_c}{F_c} - N_0\right) e^{k_0 F_c t}, \qquad F = \frac{F_0 F_c N_c}{N_c F_0 - (F_0 N_c - N_0 F_c) e^{k_0 F_c t}}. \tag{1.13}$$

This solution is valid until $F = F_m$, which implies $0 \le t \le t_1$ where

$$t_1 = \frac{1}{k_0 F_c} \log\left(\frac{F_0 N_c (F_m - F_c)}{F_m (F_0 N_c - N_0 F_c)}\right). \tag{1.14}$$

For times beyond t_1, $F = F_m$ and so the evolution of N follows $\dot{N} = -k_0(F_m - F_c)N$, which gives

$$N(t) = \frac{F_0 N_c}{F_m} e^{-k_0(F_m - F_c)(t - t_1)}, \tag{1.15}$$

since (1.13) and (1.14) together imply $N(t_1) = F_0 N_c / F_m$. The overall loss of kidney function thus follows a more smooth sigmoidal shape, with accelerating loss being followed by a more gentle relaxation towards $N = 0$. In this case there is no finite time when $N = 0$.

2 Modelling the swelling of kidney/glomeruli

In this model we explicitly include the effect of some disease which is continuously removing functioning nephrons at a constant background rate of α_0. In addition we assume that functioning nephrons are killed due to sclerosis, that is, the accumulation of debris such as polymers which inhibit their functioning. Also, we assume that nephrons die when the flow rate which they are expected to process exceeds a certain critical level. Modelling the effect of sclerosis on kidney function is discussed in Chaturvedi & Insana [1].

We denote the amount of sclerosis by S, and measure this as an average surface area, the average being taken over all functioning glomeruli. The flow rate we denote by V,

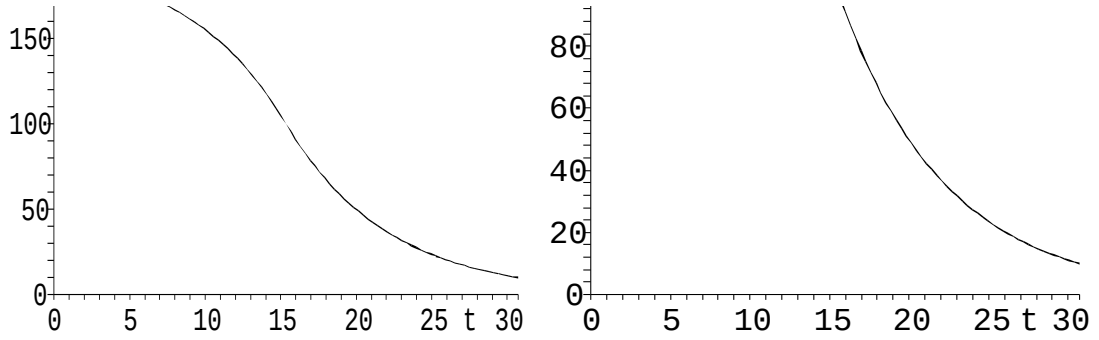

Figure 4: Solution to Model 1c. On the left the number of functioning glomeruli is plotted in thousands; on the right, the total GFR is plotted $G = NF$. Parameter values: $k_0 = 300$, $N_0 = 190000$, $N_c = 200000$, $F_c = 1/2000$, $F_0 = 1/2000$, $F_c = 100/F_0$, $F_m = 1/1000$. In this case the switch from the first to the second phases occurs at approximately $t = 15$, where $N = 100000$.

and V_0 denotes the critical rate above which nephrons die. Thus in place of (1.1) we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -k(A, V, S)N, \tag{2.1}$$

with

$$k(A, V, S) = \alpha_0 + \alpha_1 S + \alpha_2(V - V_0). \tag{2.2}$$

We assume that the progress of the disease is as follows: first an increased pressure causes the glomeruli to swell, increasing the surface area available for filtration to occur across. This enlarged filtration area is then susceptible to sclerosis, that is, the destructive accumulation of debris, which reduces the effective surface area available for filtration. Our variable $A(t)$ is an average surface area of a glomerulus, which can increase/decrease to accommodate the required GFR, and is thus typically G_H/NV in a healthy person. However, as the disease progresses the required area becomes increasingly large which is unphysical, and so we impose an upper limit, A_m, above which A cannot increase. Thus we propose

$$A(t) = \min\left\{\frac{G_H}{NV}, A_m\right\}. \tag{2.3}$$

The flow rate V is assumed to take some constant value V_0 in the first phase of the process, where the kidney has spare processing capacity. In the second phase, we assume that V increases in an attempt to maintain the GFR, however, this cannot rise to arbitrarily high values, so we also impose and upper limit on V of V_m. Thus we define

$$V(t) = \begin{cases} V_0 & \text{if } A(t) < A_m \\ \dfrac{G_H}{N(A-S)} & \text{if } A(t) = A_m \text{ and } \frac{G_H}{N(A-S)} \le V_m \\ V_m & \text{if } A(t) = A_m \text{ and } \frac{G_H}{N(A-S)} > V_m. \end{cases} \tag{2.4}$$

The final component of the model requires us to specify how quickly debris is deposited, that is the rate of sclerosis. We propose

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \beta(A - S)H(A - A_m), \tag{2.5}$$

where $H(\cdot)$ is the Heaviside function. This closes the model, and so we now describe its solution.

2.1 Solution in phase I

We aim to solve (2.1)–(2.5) subject to the initial conditions

$$S = 0, \qquad V = V_0, \qquad A = \frac{G_H}{NV_0}, \qquad N = N_0, \tag{2.6}$$

with $N_0 > G_H/A_m V_0$ so that $G_H/NV < A_m$. The solution of $\dot{N} = -\alpha_0 N$ (2.1) leads to

$$N = N_0 e^{-\alpha_0 t}, \qquad A = \frac{G_H}{NV_0} = \frac{G_H e^{\alpha_0 t}}{N_0 V_0}, \qquad S = 0, \qquad V = V_0. \tag{2.7}$$

This solution is valid until $A = A_m$, which occurs when $t = t_1$ given by

$$t_1 = \frac{1}{\alpha_0} \log\left(\frac{A_m N_0 V_0}{G_H}\right). \tag{2.8}$$

At this point in time, $N(t) = N(t_1) = G_H/A_m V_0$. In phase I, the total GFR $G(t) = NVA = G_H$, the constant required for a healthy individual.

2.2 Solution in phase II

Phase I ends due to $A(t)$ reaching A_m, thus in phase II, the glomeruli are stretched to their uppermost limit, $A = A_m$, and the available surface area for filtration undergoes no further increase. Rather, the *effective* surface area for filtration now decreases due to the build up of deposited debris, which is measured by the variable S satisfying $\dot{S} = \beta(A_m - S)$. Solving the system (2.1)–(2.5), we have

$$A = A_m, \qquad S = A_m(1 - e^{-\beta(t-t_1)}), \qquad V = \frac{G_H e^{\beta(t-t_1)}}{NA_m}. \tag{2.9}$$

The equation for the number of functioning nephrons is then

$$\frac{\mathrm{d}N}{\mathrm{d}t} + \left(\alpha_0 + \alpha_1 A_m(1 - e^{-\beta(t-t_1)}) - \alpha_2 V_0\right) N = -\frac{\alpha_2 G_H e^{\beta(t-t_1)}}{A_m}. \tag{2.10}$$

This can be solved by use of the integrating factor $e^{f(t)}$ where

$$f(t) = (\alpha_0 + \alpha_1 A_m - \alpha_2 V_0)(t - t_1) + \frac{\alpha_1 A_m e^{-\beta(t-t_1)}}{\beta}, \tag{2.11}$$

which implies

$$N(t) = \frac{G_H e^{-f(t)}}{A_m}\left[\frac{e^{\alpha_1 A_m/\beta}}{V_0} - \alpha_2 \int_{t_1}^{t} e^{\beta(s-t_1)+f(s)}\,\mathrm{d}s\right]. \tag{2.12}$$

This gives a more rapid decrease in the number of functioning glomeruli, $N(t)$.

2.3 Solution in phase III

This phase differs from phase II only in that V is now capped at its upper limit $V = V_m$. The effect of this is that the total required GFR $G(t) = G_H$ can no longer be produced. Thus, although the number of functioning glomeruli was reducing rapidly in the phase II, it is only now in phase III that the GFR is seen to reduce.

3 Model 3 - a distribution of glomeruli

3.1 Model formulation

This model is based on ideas from the modelling of age-structured populations. Instead of age, we assign to each nephron a rate at which it processes urine, r, so we introduce $n(r,t)$ as the number of nephrons which are processing urine at a rate r at time t. We assume that r lies in the range $0 < r < R$ and that requiring a nephron to process at a rate $r > R$ causes it to die.

We recover quantities used in the above models by summing over all rates

$$N(t) = \int_0^R n(r,t)\,\mathrm{d}r, \qquad G(t) = \min\left\{G_H, \int_0^R r\,n(r,t)\,\mathrm{d}r\right\}. \tag{3.1}$$

Due to the progression of disease, we assume that nephrons die, and the filtration rate required of each nephron steadily increases. This leads to the PDE

$$\frac{\partial n}{\partial t} + \beta\frac{\partial n}{\partial r}\left(\frac{G}{N} - r_c\right)_+ = 0. \tag{3.2}$$

The effect of this term is that nephrons $n(r,t)$ are advected in r-space towards larger r values. A kidney in which most of the glomeruli are operating at large values of the filtration rate r corresponds to a severely damaged kidney, thus the average value of r can be viewed as a measure of damage to a kidney, as well as the average filtration rate.

Equations such as (3.2) can be solved by the method of characteristics. The condition that no new nephrons/glomeruli can be created translates into the boundary condition at $r = 0$ of $n(0,t) = 0$.

3.2 Uniform distribution of glomeruli

We assume initial data of the form $n(r,0) = n_0$, a constant for all $r < R$. Since the characteristics of (3.2) are either vertical in (r,t)-space (i.e. r =const.) or point from $r = 0$ into $r > 0$, then we need a boundary condition on $r = 0$. The condition that no new glomeruli can be formed implies that this condition should be $n(0,t) = 0$. The solution for all time then has the form

$$n(r,t) = n_0 H(r - s(t)), \tag{3.3}$$

where $H(\cdot)$ is the Heaviside function and n_0 is a constant, this solution is illustrated in Figure 5. This solution implies that N and G are given by

$$N(t) = n_0(R - s(t)), \qquad \text{and} \quad G(t) = \min\{G_H, \tfrac{1}{2}n_0(R^2 - s(t)^2)\}, \tag{3.4}$$

respectively. An evolution equation for the quantity $s(t)$ can be determined from the integral for $N(t)$. From the above, we have $\dot{N} = -n_0\dot{s}$. Combining this with the result of differentiating (3.1) and using (3.2) we obtain

$$\frac{\mathrm{d}s}{\mathrm{d}t} = \beta\left(\frac{G}{N} - r_c\right)_+. \tag{3.5}$$

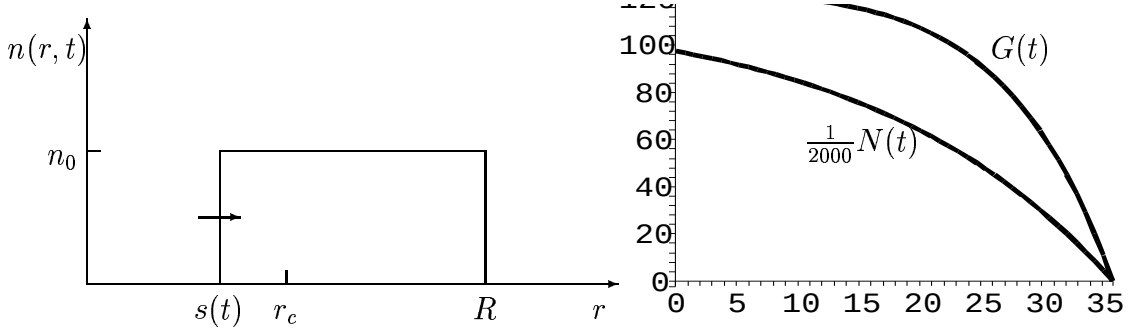

Figure 5: Illustration of the possible solutions for Model 3. On the left: an illustration of the uniform distribution we assume for $n(r,t)$, where $s(t)$ increases with time. On the right, the resulting curves for $N(t)$ and $G(t)$ are plotted against t. The upper curve corresponds to $G(t)$, and the lower curve to $N(t)/2000$, thus this starts just below 200000 and decays to zero. Other parameters are $b = 0.1$, $G_H = 100$, $r_c = 1/2000$, $R = 1/800$, $s_0 = 0$. The solutions are described in Section 3.2.

3.2.1 Final, exponential decay

When the initial data is uniform across r, we have $N_0 = Rn_0$ and maximum attainable GFR is given by $G = \frac{1}{2}R^2 n_0$. If we assume that $\frac{1}{2}n_0R^2 < G_H$, then this is value of G used in the advection term $(G/N - r_c)$. This implies $G/N = \frac{1}{2}R$ so if $R > 2r_c$ then the kidney suffers further damage and the system evolves according to (3.5) which can be simplified to

$$\frac{\mathrm{d}s}{\mathrm{d}t} = \tfrac{1}{2}\beta(s + R - 2r_c). \tag{3.6}$$

This is solved by

$$s(t) = (R - 2r_c)(e^{\beta t/2} - 1). \tag{3.7}$$

This solution is physically relevant for the case $R > 2r_c$, that is, when the maximum processing capacity per nephron (R) is more than twice the level at which damage is caused (r_c).

If $R < 2r_c$ then starting from $s(0) = 0$, the characteristic $\beta(G/N - r_c)_+ = \beta(\frac{1}{2}R - r_c)_+ = 0$ and so $s(t) = 0$ for all t. The physical interpretation of this solution, and in particular the effect of $s(t)$ increasing with time is that the number of functioning nephrons reduces $(N \searrow)$, the total processing capacity of the kidney also decays $(G \searrow)$, but in such a way that the average amount of fluid processed by each nephron *increases* $(G/N \nearrow)$. In the case $R < 2r_c$, starting from $s(0) = 0$, we have $s(t) = 0$ for all $t > 0$, so that is no damage is caused. However, if we excise a portion of the kidney, or assume initial conditions of the form (3.3) with $s(0) = s_0 > 0$, then a nontrivial solution is possible provided $s_0 > 2r_c - R$. The solution is then

$$s(t) = (s_0 + R - 2r_c)e^{\beta t/2} + (2r_c - R). \tag{3.8}$$

The final time at which the final glomeruli dies is then

$$t_1 = \frac{2}{\beta}\log\left(\frac{2(R - r_c)}{(R - 2r_c + s_0)}\right). \tag{3.9}$$

3.2.2 Alternative small time solution

It is possible that the solution (3.3) holds but with $G = G_H$ (since $\int_0^R rn(r,t)\,\mathrm{d}r > G_H$) for an initial phase. During this phase damage is still caused, that is, the advection

term is still active. Again the differential equation for $s(t)$ is found from (3.5) which, with $G = G_H$, simplifies to

$$\frac{\mathrm{d}s}{\mathrm{d}t} = \beta\left(\frac{G_H}{n_0(R-s)} - r_c\right). \tag{3.10}$$

For a non-trivial solution we require an initial condition $s(0) = s_0$ with

$$s_0 > R - \frac{G_H}{n_0 r_c}. \tag{3.11}$$

Assuming this condition is met, (3.10) has the implicit solution

$$\beta r_c t = s_0 - s + \frac{G_H}{n_0 r_c}\log\left(\frac{G_H - r_c n_0(R-s)}{G_H - r_c n_0(R-s_0)}\right). \tag{3.12}$$

This solution is valid until $s(t)$ grows to the magnitude where $\int_0^R rn(r,t) = \frac{1}{2}n_0(R^2 - s^2) = G_H$. At this point, G (3.1) switches from being G_H and takes on the time-dependent value $\frac{1}{2}n_0(R^2 - s^2)$ and the solution for $s(t)$ switches from (3.12) to the exponentially growing solution of the form (3.7).

During this phase of disease, the number of functioning nephrons reduces ($N \searrow$) but the kidney retains enough function to process enough fluid as required by the body (that is, the total GFR $G(t) = G_H$, a constant). The overall effect of N reducing and G remaining constant is that the average amount of fluid processed by each nephron increases ($G/N \nearrow$). Over this time $G/N > r_c$, that is the average rate at which fluid is processed is high enough to cause further damage to the kidney, so nephrons continue to die.

3.3 A more realistic distribution of glomeruli

The advantage of the form of the PDE (3.2) is that all nephrons are advected in r-space at the same rate. The problem is then in effect a travelling wave, with unknown time-dependent speed which needs to be found in a self-consistent manner as part of the solution. The initial condition (3.3) is probably unphysical since it assumes that, initially at least, there are as many glomeruli filtering at a negligibly small rate as at any other rate.

Thus here we propose an alternative initial condition, where the population of glomeruli operate with a more realistic distribution of filtration rates. In general we allow initial data of the form $n(r,0) = n_0(r)$ with $n_0(r)$ differentiable. To be specific, we postulate initial data

$$n(r,t) = \frac{n_0\sigma}{2}\mathrm{sech}^2(\sigma(r-\mu)), \tag{3.13}$$

with $\mu < R$, and σ large enough such that at $t = 0$ the distribution decays well inside the region $0 < r < R$. This implies $N(0) = n_0$. As damage is inflicted on the kidney, we expect the distribution to move to larger r-values, which simply corresponds to μ being a monotonically increasing function of time. The solution (3.13) is illustrated in Figure 6.

The integral N can be evaluated exactly, and we shall assume that the tail in $r < 0$ is ignorable and so use the approximation

$$\begin{aligned} N &= \tfrac{1}{2}n_0\left[\tanh(\sigma(R-\mu)) - \tanh(-\sigma\mu)\right] \\ &\sim \tfrac{1}{2}n_0\left(1 + \tanh(\sigma(R-\mu))\right) = \frac{n_0}{1+e^{-2\sigma(R-\mu)}}. \end{aligned} \tag{3.14}$$

An equation for the evolution of the quantity $\mu(t)$ can be found by differentiating both this expression, giving $\dot{N} = -2n_0\dot{\mu}e^{-2\sigma(R-\mu)}$, and differentiating the integral form (3.1), which leads to

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\beta\left(\frac{G}{N} - r_c\right)_+ \frac{n_0}{2\sigma}\left[\mathrm{sech}^2(\sigma(R-\mu)) - \mathrm{sech}^2(-\sigma\mu)\right]. \tag{3.15}$$

Combining the two approximations, again ignoring the second sech^2 term in the above expression since it will be small, we obtain

$$\frac{\mathrm{d}\mu}{\mathrm{d}t} = \beta\left(\frac{G}{N} - r_c\right)_+. \tag{3.16}$$

It is this equation we shall aim to solve in the remainder of this section. Through the approximations we have made, we have obtained essentially the same equation for $\mu(t)$ as we had for $s(t)$ in section 3.2, namely equation (3.5).

3.3.1 More realistic distribution - solution in phase I

In the first phase of disease, there is sufficient capacity in the kidney that, although glomeruli are dying and the distribution is aging, the kidney can maintain a GFR of G_H. With $G(t) = G_H$ being constant and $N(t)$ given by (3.15), equation (3.16) is integrable and we have the solution

$$e^{2\sigma(R-\mu(t))} = e^{2\sigma(R-\mu_0)-2\sigma\beta(G_H-r_cn_0)t/n_0} - \frac{G_H(1-e^{-2\sigma\beta(G_H-r_cn_0)t/n_0})}{G_H - 2r_cn_0}, \tag{3.17}$$

where the initial condition $\mu(0) = \mu_0$ has been imposed.

3.3.2 More realistic distribution - solution in phase II

In the second phase, the kidney is working at full capacity, and this is supplies a lower GFR than G_H, thus we have $G = \int_0^R rn(r,t)\,\mathrm{d}r$. Using the form (3.13), this can be calculated as

$$G(t) = \frac{n_0R}{1+e^{-2\sigma(R-\mu(t))}} - \frac{n_0}{2\sigma}\log\left(1+e^{2\sigma(R-\mu(t))}\right). \tag{3.18}$$

Hence

$$\frac{G}{N} = R - \frac{(1+e^{-2\sigma(R-\mu)})}{2\sigma}\log\left(1+e^{2\sigma(R-\mu)}\right). \tag{3.19}$$

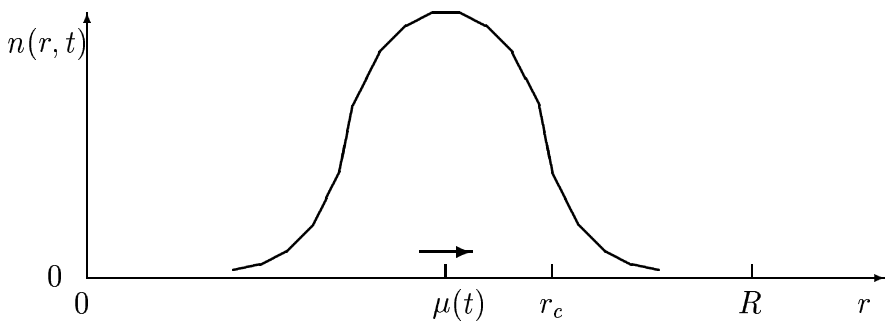

Figure 6: A more realistic distribution of rates of processing for a population of glomeruli. The solution for this case is discussed in Section 3.3.

The ratio G/N is the mean of the distribution over the region $0 < r < R$, assuming this mean is above r_c, (which is to be expected if $G < G_H$) then further damage to the kidney is caused, and the distribution evolves according to (3.16).

If this happens whilst $\sigma(R-\mu) \gg 1$ then (3.16) and (3.19) simplify to $\dot{\mu} = \beta(\mu - r_c)$ and we have exponential growth in μ, according to

$$\mu(t) = r_c + \mu_1 e^{\beta t}, \tag{3.20}$$

for some constant μ_1. During this phase of the process, the total number of nephrons, N, varies according to

$$N(t) \sim \frac{n_0}{(1 + e^{2\sigma(R-\mu(t))}} \sim n_0 - n_0 e^{-2\sigma(R-\mu(t))}, \tag{3.21}$$

which represents a very slow loss. The evolution of the total GFR is more complex: formally, in the asymptotic limit $\sigma(R-\mu) \gg 1$, we have

$$G(t) \sim n_0\mu(t) - n_0\left(R + \frac{1}{2\sigma}\right) e^{-2\sigma(R-\mu(t))}. \tag{3.22}$$

The leading order term $G \sim n_0\mu$ suggests that the GFR *grows* linearly with μ, hence exponentially in time (since $\mu(t)$ follows (3.20)); however, for realistic parameter values, the correction term could be more relevant. This term causes $G(t)$ to decay exponentially in μ. This term would give extremely rapid reduction in time, t.

In the final stages of the decay of the kidney, we expect $\mu > R$ and then using the approximation $\sigma(\mu - R) \gg 1$ yields $\dot{\mu} = \beta(R - r_c - 1/2\sigma)$, thus we have a final decay in which μ grows linearly, according to

$$\mu(t) \sim \mu_2 + \beta\left(R - r_c - \frac{1}{2\sigma}\right) t, \tag{3.23}$$

and so $N(t)$ decays exponentially with $N(t) \sim n_0 e^{2\sigma(R-\mu(t))}$, and $G(t)$ also decays exponentially with $G(t) \sim n_0(R - 1/2\sigma)e^{2\sigma(R-\mu(t))}$.

4 Conclusions

In this report we have presented and analysed a series of models of progressive kidney damage. The simplest models (Section 1) are based on population models with a death rate which depends on the average filtration rate of each glomerulus; when this rate exceeds a certain level, we assume that nephrons are lost from the system. These models produce graphs which have the correct qualitative behaviour, and by tuning parameters, it should be straightforward to fit to data. In Section 2 a second, more detailed, level of modelling sought to provide some understanding of the process by which glomeruli become sclerosed. We assumed that this was due to a combination of increased pressure which aims to improve the flow rate through the glomeruli, but has the detrimental side-effect of causing the glomerulus to swell and become sclerosed. Finally we proposed a model in which the population of glomeruli were assumed to function at a variety of filtration rates. As the kidneys suffered damage, those glomeruli filtering at the highest rates die, and others operate at increased rates in an attempt to still provide the body's required GFR.

These models also showed the expected temporal behaviour of a slow phase where glomeruli are slowly lost, followed by a much more rapid decline in later stages of disease.

Provided the parameters all chosen correctly, all the models can be made to satisfy the condition that upto 80% of the glomeruli can be removed and the remaining glomeruli filter at an increased rate without the kidney suffering further damage. However, when more than 80% is removed, the kidney then suffers progressive damage until all function is lost. Typically there is a slow phase where the kidney suffers damage, but is able to filter enough fluid for the body; there then follows a more rapid decline in function as the kidney is no longer able to filter the required amount of fluid.

There are many ways in which the models presented here could be improved, these are left for future work. Desirable improvements to the model described in Section 2 include smoothing out the corners in graphs of A, V against time when the solution switches from one branch of, for example, (2.3) or (2.4) to the other. The model could be made more realistic by allowing both A and V to vary simultaneously. This would require a further constitutive law to prescribe how A and V (and possibly blood pressure also) are linked.

It would be good to generalise model in Section 3 so that the advection term was greater for smaller r, and less for larger r; i.e. of the form $\beta(r) = \beta_0(R_1 + R - r)$. Unfortunately the advection rates for the distribution of glomeruli are then different, and so the ansatz $n(r,t) = n_0(r - s(t))$ no longer produces a valid solution to the PDE. Solution of the model when $\beta = \beta(r)$ becomes rather complicated. There is also the problem that generalising the model in this way introduces more parameters, and it is uncertain whether there is enough data in a form from which all the parameters currently in the model can be determined.

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