

reference to any further properties of the peritubular capillaries. This would not have been true if different assumptions about  $\text{Na}^+$  and water transport across the capillary walls had been made.

We begin the study of Henle's loop by deriving a differential equation for the interstitial concentration  $c(x)$ . Note that (4.3.1) and (4.3.2) can be rewritten using (4.3.3) and (4.3.8) as follows:

$$0 = (dQ_1/dx) + f_{\text{Na}}^*/c(x), \quad (4.3.9)$$

$$0 = (d/dx)(Q_1c). \quad (4.3.10)$$

Now, (4.3.10) implies that  $Q_1c = \text{constant}$ . We use this to get an expression for  $Q_1(x)$  in terms of  $c(x)$ :

$$Q_1(x) = Q_1(0)c(0)/c(x). \quad (4.3.11)$$

Note that  $c(0)$  is the  $\text{Na}^+$  concentration  $c(x)$  in the fluid entering the loop of Henle from the proximal tubule. This is the same as the  $\text{Na}^+$  concentration in blood plasma, and we can therefore regard  $c(0)$  as given. Similarly,  $Q_1(0)$  is the volume rate of flow entering the loop. This flow is *less* than the filtration rate by the total amount of fluid reabsorbed in the proximal tubule per unit time. We shall see later how  $Q_1(0)$  is determined.

Another consequence of (4.3.10) is that

$$c \frac{dQ_1}{dx} = -Q_1 \frac{dc}{dx} = -Q_1(0)c(0) \frac{dc/dx}{c(x)}. \quad (4.3.12)$$

It follows that (4.3.9) can be rewritten in the form

$$\frac{dc}{dx} = \frac{f_{\text{Na}}^*c}{(Q_1(0)c(0))}, \quad (4.3.13)$$

which implies that

$$c(x) = c(0) \exp\left(\frac{f_{\text{Na}}^*x}{Q_1(0)c(0)}\right) \quad (4.3.14)$$

and, in particular, that

$$c(L) = c(0) \exp\left(\frac{f_{\text{Na}}^*L}{Q_1(0)c(0)}\right). \quad (4.3.15)$$

Note that  $f_{\text{Na}}^*L$  is the total rate at which  $\text{Na}^+$  is actively pumped out through the walls of the ascending limb of Henle's loop, while  $Q_1(0)c(0)$  is the rate at which  $\text{Na}^+$  enters the loop from the proximal tubule. Thus, the ratio of these fluxes

$$\alpha = \frac{f_{\text{Na}}^*L}{Q_1(0)c(0)} < 1 \quad (4.3.16)$$

determines the maximum concentrating ability of the model nephron for  $\text{Na}^+$  through the equation

$$c(L) = c(0) \exp(\alpha). \quad (4.3.17)$$

We are now ready to consider the ascending limb of Henle's loop. Since this tubule is impermeable to water (equation 4.3.4) we have

$$Q_2(x) = Q_2(L) = -Q_1(L) = -Q_1(0)c(0)/c(L) = -Q_1(0) \exp(-\alpha). \quad (4.3.18)$$

Since  $Q_2$  is constant, equation (4.3.5) reduces to

$$\frac{dc}{dx} = \frac{f_{\text{Na}}^*}{-Q_2} = \frac{f_{\text{Na}}^* \exp(\alpha)}{Q_1(0)}. \quad (4.3.19)$$

It follows that

$$c_2(x) = c_2(L) + (x-L)f_{\text{Na}}^* \exp(\alpha)/Q_1(0). \quad (4.3.20)$$

But,  $c_2(L) = c(0) \exp(\alpha)$ . Thus,

$$c_2(x) = c(0) \exp(\alpha) + (x-L)f_{\text{Na}}^* \exp(\alpha)/Q_1(0). \quad (4.3.21)$$

In particular,

$$\begin{aligned} c_2(0) &= c(0) \exp(\alpha) + (0-L)f_{\text{Na}}^* \exp(\alpha)/Q_1(0) \\ &= c(0) \exp(\alpha)(1-\alpha). \end{aligned} \quad (4.3.22)$$

It is now easy to check (see Exercise 4.2) that  $\exp(\alpha)(1-\alpha) < 1$  when  $\alpha \neq 0$ . Thus,  $c_2(0) < c(0)$ , and the fluid leaving the top of the ascending limb is more dilute than blood plasma.

We have succeeded in expressing the outputs of Henle's loop in terms of its inputs. In the next section we shall find a good physiological reason for reversing this procedure. That is, we will find that the nephron actually adjusts  $Q_1(0)$  to achieve a specified  $\text{Na}^+$  concentration  $c_2(0)$  at the top of the ascending limb. Thus, we should regard  $c_2(0)$  as being a parameter, and we should express  $Q_1(0)$  in terms of it.

#### 4.4 The Juxtaglomerular Apparatus and the Renin-Angiotensin System

Near the top of the ascending limb of Henle's loop there is a specialized cluster of cells called the *juxtaglomerular apparatus*. These cells monitor the tubular fluid and secrete a hormone, *renin*, into the afferent arteriole just before it enters the glomerulus. Renin is converted in the blood to *angiotensin*, a potent vasoconstrictor, i.e., a substance that stimulates the constriction of blood vessels. Although the details are not certain, it is a plausible hypothesis that the cells of the juxtaglomerular apparatus monitor specifically the  $\text{Na}^+$  concentration at the top of the ascending limb, and that they secrete enough renin to make the glomerular filtration, and perhaps reabsorption from the proximal tubule, proceed at whatever rate is needed to achieve a target level  $\text{Na}^+$  concentration at that site.

Evidence that such a feedback mechanism is in operation comes from experiments of Thraau, who was able to shut down flow in the proximal nephron by perfusing the distal nephron with salt solutions of higher than normal concentration.

We shall model this feedback mechanism in the simplest possible way: We assume that the inflow  $Q_1(0)$  to the loop of Henle takes on whatever value is needed to satisfy the equation

$$c_2(0) = c^*, \quad (4.4.1)$$

where  $c^* < c(0)$  is the target concentration sought by the juxtaglomerular apparatus. Thus, we do not model the details of the renin-angiotensin system. We simply assume that it is working, and we study its effects on the performance of the nephron.

Substituting (4.3.22) in (4.4.1), we get

$$a = \exp(\alpha)(1 - \alpha), \quad (4.4.2)$$

where

$$a = c^*/c(0) < 1. \quad (4.4.3)$$

Here  $a$  is regarded as known ( $0 < a < 1$ ), so (4.4.2) is an equation for  $\alpha$  and hence for  $Q_1(0)$ .

The graphical solution of (4.4.2) is discussed in Exercise 4.3, where it is shown that (4.4.2) has a unique positive solution for each  $a$  such that  $0 < a < 1$  and that the solution satisfies  $0 < \alpha < 1$ . Armed with this knowledge, we can see directly from (4.4.2) that as  $a \rightarrow 0$ ,  $\alpha \rightarrow 1$ . Thus, for small values of  $a$ ,

$$\alpha \approx 1, \quad (4.4.4)$$

$$1 - \alpha \approx a/\exp(1) = a/e. \quad (4.4.5)$$

from the definition of  $\alpha$ , (4.3.16), we see that  $\alpha \approx 1$  means that the  $\text{Na}^+$  flux entering the loop of Henle has been adjusted to the pumping capacity of the ascending limb.

We can now rewrite the results of the previous section with  $c^*$  as a parameter under the assumption that  $a$  is small. We have

$$Q_1(0) = f_{\text{Na}}^* L/c(0), \quad (4.4.6)$$

$$-Q_2 = f_{\text{Na}}^* L/(ec(0)), \quad (4.4.7)$$

$$c(L) = ec(0), \quad (4.4.8)$$

$$c_2(0) = c^*. \quad (4.4.9)$$

These simple results summarize the behavior of the model of Henle's loop as controlled by the juxtaglomerular apparatus. Equation (4.4.6) states that the inflow to Henle's loop is adjusted so that the amount of  $\text{Na}^+$  in entering the loop per unit time ( $Q_1(0)c(0)$ ) is equal to the amount that can be pumped out of the ascending limb per unit time ( $f_{\text{Na}}^* L$ ). Equation (4.4.7)

Table 4.1. Outputs of the Model Nephron

	Diluting Mode (ADH Absent)	Concentrating Mode (ADH Present)
$\text{Na}^+$ concentration in urine	$c^*$	$e c(0)$
Rate of $\text{H}_2\text{O}$ excretion	$f_{\text{Na}}^* L/(ec(0))$	$f_{\text{Na}}^* Lc^*/(ec(0))^2$
Rate of $\text{Na}^+$ excretion	$f_{\text{Na}}^* L c^*/(ec(0))$	$f_{\text{Na}}^* Lc^*/(ec(0))$

states that the flow ( $-Q_2$ ) in the ascending limb of the loop is smaller by a factor of  $e \approx 2.7$  than the flow entering the loop ( $Q_1(0)$ ). The difference, of course, was reabsorbed from the descending limb and carried away by the peritubular capillaries along with the  $\text{Na}^+$  pumped out of the ascending limb. Equation (4.4.8) states that the  $\text{Na}^+$  concentration outside the tubules (and also in the descending limb of Henle's loop) increases by a factor of  $e$  as we follow the descending limb from its origin (where the  $\text{Na}^+$  concentration is  $c(0)$ , the same as in blood plasma) to its turning point (where the  $\text{Na}^+$  concentration is  $c(L)$ ). Finally, equation (4.4.9) states that the  $\text{Na}^+$  concentration in the fluid leaving the loop of Henle at the top of the ascending limb has the "target"  $\text{Na}^+$  concentration  $c^*$ , which was indirectly established by the flow regulation achieved by the juxtaglomerular apparatus. Equations (4.4.6) through (4.4.9) are approximate results that are valid only when  $c^* \ll c(0)$ .

## 4.5 The Distal Tubule and Collecting Duct: Concentrating and Diluting Modes

We now come to the stage in the formation of urine where a decision has to be made whether to excrete a large volume of dilute urine or a small volume of concentrated urine. The hormone that determines which possibility will occur is antidiuretic hormone (ADH). When ADH is absent, we assume that the distal tubule and the collecting ducts are simple conduits, impermeable to both salt and water. In these circumstances, the fluid that leaves the top of the ascending limb becomes urine without further modification. Its properties are summarized in the first column of Table 4.1.

When ADH is present, the situation is more complicated. The effect of ADH is to make the distal tubule and the collecting duct permeable to water. We assume that this permeability is so great that equilibrium is achieved at every stage. In the distal convoluted tubule, then, enough water is withdrawn to make the  $\text{Na}^+$  concentration equal to that of the blood plasma. Then, in the collecting duct, enough water is withdrawn to equilibrate with  $c(x)$  at each  $x$ . We make the approximation that this water flux is negligible compared to the flux coming out of the descending limb

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{see Exercise 4.6}. It follows that the concentration of  $\text{Na}^+$  in the urine is  $c(L) = ec(0)$ . To figure out the volume rate of urine production, we first note that since only water is withdrawn, the  $\text{Na}^+$  flux at the end of the collecting duct must be the same as that leaving Henle's loop. This  $\text{Na}^+$  flux is given by

$$-Q_2c^* = f_{\text{Na}}^* Lc^* / (ec(0)). \quad (4.5.1)$$

Thus, the flow leaving the collecting duct when ADH is present must be

$$Q_3(L) = -Q_2c^* / c(L) = f_{\text{Na}}^* Lc^* / (ec(0))^2. \quad (4.5.2)$$

These results are entered in the second column of Table 4.1.

Comparison of the two modes of operation of the model nephron can be summarized as follows: First, the urine is more dilute than blood plasma when ADH is absent and more concentrated when ADH is present. Second, the volume rate of flow is much smaller when ADH is present by a factor of  $c^*/ec(0)$ . The rate at which  $\text{Na}^+$  is excreted is the same in both cases, however.

Thus, the ADH mechanism cannot be used to regulate the total  $\text{Na}^+$  content of the body. It can be used to regulate the  $\text{Na}^+$  concentration of the blood plasma by excreting varying amounts of water in response to fluctuations in the plasma concentration of  $\text{Na}^+$ .

#### 4.6 Remarks on the Significance of the Juxtglomerular Apparatus

The filtration rate in the kidney is about 100 times the rate of urine formation. Therefore, 99% of the filtrate must be reabsorbed, and a 1% error in the reabsorption rate results in a 100% error in the rate of urine formation. A nephron in which filtration is maintained, but reabsorption fails completely, excretes about 100 times as much urine as it should. It is inconceivable that such large errors would be tolerated. Clearly, the kidney needs control mechanisms that adjust the input to each nephron according to the capacity of the nephron for reabsorption of  $\text{Na}^+$  and water.

We have seen that the juxtglomerular apparatus can achieve this end by monitoring the  $\text{Na}^+$  concentration at the top of the ascending limb of Henle's loop. When this has been done and when the filtration rate has been adjusted accordingly in each nephron, a heterogeneous population of nephrons can function in a coordinated fashion as easily as a homogeneous population. To see this, note that the concentrations in Table 4.1 are independent of the reabsorption capacity  $f_{\text{Na}}^* L$ , while the rates of excretion of both  $\text{Na}^+$  and water are proportional to that capacity.

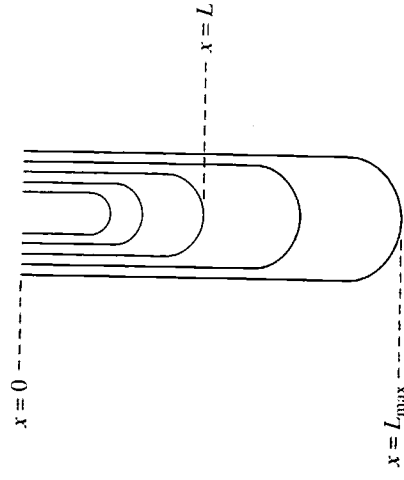


Figure 4.4. An interacting population of loops of Henle whose lengths  $L$  vary from 0 to  $L_{\text{max}}$ . Note that at a given level  $x$  one sees only those loops whose lengths are at least equal to  $x$ .

Thus, each nephron contributes what it can to the production of a homogeneous urine. Coordinated performance of this kind would be impossible without the juxtglomerular apparatus.

#### 4.7 How Nephrons Do Better Than a Factor of $e$

The model nephron considered up to now in this chapter has the property that it cannot produce a urine in which the solute concentration is greater than  $e \times$  the solute concentration in blood plasma, where the transcendental number  $e$  is approximately 2.7. No such limitation is observed in real kidneys, so we need to ask what feature of the foregoing model needs to be modified to account for the actual concentrating ability of the kidney. The answer, which is truly astonishing, was discovered by Harold Layton. It turns out that no modification at all in the nephron model is required. Instead, different nephrons can work together in a kind of "cascade" to produce higher solute concentrations in the urine than any one nephron could produce by itself. In order to do so, however, the nephrons must be of *different lengths*, and they must share the *same interstitial space*.

Let us consider, therefore, a population of loops of Henle, as shown in Figure 4.4. Each of these loops begins and ends at  $x = 0$ , and penetrates to a depth  $x = L$ , but  $L$  is different for the different loops in the population. We assume that  $L$  can take any value in the interval  $0 \leq L \leq L_{\text{max}}$ , for some fixed  $L_{\text{max}}$ , which in practice could be the "radius" of the kidney, i.e., the combined thickness of the cortex and medulla.

We shall describe the population of loops of Henle by the population density function  $\rho(L)$ , which has the following meaning:

$$\int_{L_1}^{L_2} \rho(L) dL = \text{number of loops with } L \text{ in the interval } (L_1, L_2). \quad (4.7.1)$$

The integral over all  $L$ ,  $\int_0^{L_{\max}} \rho(L) dL$ , is the total number of loops in the population.

Each loop has the same properties as considered earlier in this chapter. In particular, all of the descending limbs have walls that are freely permeable to water but impermeable to  $\text{Na}^+$ , and all of the ascending limbs have walls that are impermeable to water and pump  $\text{Na}^+$  out at a fixed rate  $f_{\text{Na}}^*$  per unit length of tubule. We also assume that each loop comes equipped with its own juxtaglomerular apparatus that adjusts the inflow to the loop until the concentration of  $\text{Na}^+$  at the top of the ascending limb is equal to some prescribed value  $c^*$ , independent of the length of the loop. Note that  $c^* < c_0$ , where  $c_0$  is the concentration of  $\text{Na}^+$  in blood plasma.

Since all of the loops interact with the same interstitium, the external concentration of  $\text{Na}^+$  ion is given by a single function  $c(x)$ , which remains to be determined. Because the descending limbs are freely permeable to water,  $c(x)$  is also the concentration of  $\text{Na}^+$  in each of the descending limbs, regardless of the length of that limb.

The volume flow rate along the descending limbs may be different for nephrons of different lengths, even if those flow rates are measured at the same depth  $x$ . Let us therefore define  $Q_1(x, L) =$  flow rate at  $x$  in the descending limb of a loop of length  $L$ . Similarly, let  $(f_{\text{H}_2\text{O}})_1(x, L) =$  flux of water (volume per unit time, per unit length of tubule) at  $x$  out of a descending limb whose length is  $L$ . Of course,  $Q_1(x, L)$  and  $(f_{\text{H}_2\text{O}})_1(x, L)$  are defined only for  $x \leq L$ .

We can now write down five equations that determine the behavior of the whole population of loops of Henle. These equations (which will be explained below) are as follows:

$$c(0) = c_0, \quad (4.7.2)$$

$$\frac{\partial Q_1}{\partial x}(x, L) + (f_{\text{H}_2\text{O}})_1(x, L) = 0, \quad (4.7.3)$$

$$\frac{\partial}{\partial x} (c(x)Q_1(x, L)) = 0, \quad (4.7.4)$$

$$Q_1(L, L)c(L) = f_{\text{Na}}^*L + Q_1(L, L)c^*, \quad (4.7.5)$$

$$c(x) \int_x^{L_{\max}} (f_{\text{H}_2\text{O}})_1(x, L) \rho(L) dL = f_{\text{Na}}^* \int_x^{L_{\max}} \rho(L) dL. \quad (4.7.6)$$

The symbol  $\partial/\partial x$  appearing in these equations denotes the *partial* derivative with respect to  $x$ . This is essentially the same as the familiar  $d/dx$ , also called the *ordinary* derivative, but the symbol  $\partial/\partial x$  is used when there is more than one independent variable, as a reminder to hold all other vari-

ables constant when taking the derivative with respect to  $x$ . (In our case, there is one other independent variable, namely  $L$ .)

Equation (4.7.2) simply asserts that the fluid entering all of the loops of Henle has the same  $\text{Na}^+$  concentration as blood plasma. Equation (4.7.3) expresses the conservation of volume for flows in the descending limbs in each of the loops of Henle. Equation (4.7.4) states that the transport of  $\text{Na}^+$  along each of the descending limbs is constant (independent of  $x$ ), since these descending limbs are assumed to be impermeable to  $\text{Na}^+$ . Equation (4.7.5) expresses  $\text{Na}^+$  balance for the ascending limbs. The lefthand side is the rate at which  $\text{Na}^+$  enters the ascending limb of a loop of length  $L$ , and the right-hand side is the sum of the amount of  $\text{Na}^+$  that is pumped out of the ascending limb and the amount of  $\text{Na}^+$  that makes it all the way around the loop of Henle and leaves the ascending limb at the top.

Equation (4.7.6) requires the most explanation. The integrals that appear in it extend from  $x$  to  $L_{\max}$  and therefore involve all loops of length  $x$  or greater. These are the loops that are present at level  $x$ , all others having turned before reaching this level. The integral on the righthand side is simply the *number* of loops of length at least  $x$ . This is multiplied by  $f_{\text{Na}}^*$  to get the total flux of  $\text{Na}^+$  out of ascending limbs at level  $x$ . The integral on the left-hand side is the total flux of water out of descending limbs at level  $x$ . As this water is picked up by the peritubular capillaries, it carries with it a flux of  $\text{Na}^+$  equal to the flux of water multiplied by  $c(x)$ , the local interstitial concentration of  $\text{Na}^+$ . Thus equation (4.7.6) expresses the steady-state condition that the local rate of uptake of  $\text{Na}^+$  by the peritubular capillaries must balance the local rate at which  $\text{Na}^+$  is pumped out of the ascending limbs.

We now combine the above equations to get a single equation for the interstitial concentration profile  $c(x)$ . This is done as follows. First, solve equation (4.7.5) for  $Q_1(L, L)$ ; the flow rate at the hairpin turn of a loop of length  $L$ . This gives

$$Q_1(L, L) = \frac{f_{\text{Na}}^*L}{c(L) - c^*}. \quad (4.7.7)$$

Next, from equation (4.7.4),

$$c(x)Q_1(x, L) = c(L)Q_1(L, L) = \frac{f_{\text{Na}}^*L}{1 - c^*/c(L)}, \quad (4.7.8)$$

$$Q_1(x, L) = \frac{1}{c(x)} \frac{f_{\text{Na}}^*L}{1 - c^*/c(L)}. \quad (4.7.9)$$

Then, from equation (4.7.3),

$$(f_{\text{H}_2\text{O}})_1(x, L) = -\frac{\partial Q_1}{\partial x}(x, L) = -\frac{1}{(c(x))^2} \frac{dc}{dx}(x) \frac{f_{\text{Na}}^*L}{1 - c^*/c(L)}. \quad (4.7.10)$$

Substituting this result into equation (4.7.6), and canceling  $f_{Na}^*$  and one of the factors of  $c(x)$ , we get the equation

$$\frac{1}{c(x)} \frac{dc}{dx} \int_x^{L_{\max}} \frac{L \rho(L) dL}{1 - c^*/c(L)} = \int_x^{L_{\max}} \rho(L) dL, \tag{4.7.11}$$

which can be put in the form

$$\frac{d}{dx} (\log c(x)) = \int_x^{L_{\max}} \rho(L) dL \left( \int_x^{L_{\max}} \frac{L \rho(L) dL}{1 - c^*/c(L)} \right)^{-1} \tag{4.7.12}$$

Finally, we can integrate this equation from  $x = 0$  to  $x = X$  and then apply the exponential function (which is the inverse of the natural logarithm) to both sides. Recalling the boundary condition that  $c(0) = c_0$ , i.e., that the concentration of  $Na^+$  entering each loop of Henle is the same as that in the blood plasma, we obtain

$$c(X) = c_0 \exp \left( \int_0^X \frac{\int_x^{L_{\max}} \rho(L) dL}{\int_x^{L_{\max}} \frac{L \rho(L) dL}{1 - c^*/c(L)}} dx \right). \tag{4.7.13}$$

Equation (4.7.13) is an integral equation in the unknown function  $c(x)$ , which appears on the left-hand side evaluated at  $x = X$  and on the right-hand side evaluated at  $x = L$ . (Both  $X$  and  $L$  are variable, and take on values between 0 and  $L_{\max}$ .) There is a special (or limiting) case, however, in which equation (4.7.13) reduces to a formula for  $c(X)$ . That is the case  $c^* = 0$ . Then  $c(L)$  no longer appears on the right-hand side of equation (4.7.13), and we have the formula

$$c(X) = c_0 \exp \left( \int_0^X \frac{\int_x^{L_{\max}} \rho(L) dL}{\int_x^{L_{\max}} L \rho(L) dL} dx \right). \tag{4.7.14}$$

Although this result is exact only when  $c^* = 0$ , it is approximately correct when  $c^*$  is small, i.e., when  $c^*/c_0 \ll 1$ . We shall study the behavior of this approximate solution now, and later suggest a computing project to solve the integral equation (4.7.13) in order to study the effect of nonzero  $c^*$  on the interstitial concentration profile  $c(x)$ .

As a simple example of a nephron population, consider the case in which  $\rho(L)$  is constant on the whole interval from 0 to  $L_{\max}$ , say  $\rho(L) = \rho_0$ . This means that the number of loops whose lengths fall in a given interval is just proportional to the size of that interval. Another way to say this is that the number of loops of length *at least*  $L$  declines linearly with  $L$  until that number reaches zero at  $L = L_{\max}$ . In this case, the integrals that appear in equation (4.7.14) are very easy to evaluate. We have

$$\int_x^{L_{\max}} \rho(L) dL = \rho_0 (L_{\max} - x), \tag{4.7.15}$$

$$\int_x^{L_{\max}} L \rho(L) dL = \frac{1}{2} \rho_0 (L_{\max}^2 - x^2). \tag{4.7.16}$$

Factoring the difference of squares, and combining these results, we get

$$c(X) = c_0 \exp \left( \int_0^X \frac{2}{L_{\max} + x} dx \right), \tag{4.7.17}$$

$$c(X) = c_0 \exp \left( 2 \log \frac{L_{\max} + X}{L_{\max}} \right). \tag{4.7.18}$$

Now,  $\exp(2 \log(z)) = \exp(\log(z^2)) = z^2$ , and so the above result can be simplified as

$$c(X) = c_0 \left( \frac{L_{\max} + X}{L_{\max}} \right)^2. \tag{4.7.19}$$

Note in particular that  $c(L_{\max}) = 4c_0$ , and this exceeds the concentrating ability of an isolated nephron by the factor  $4/e$  which is about 1.5, or a 50% improvement. In Exercise (4.8) you will have the opportunity to design loop-length distributions that do considerably better than this.

The theory that we have just outlined can be improved by including the effects of the collecting ducts on the concentration profile. This is in the spirit of Exercise 4.7, in which you are asked to do the same thing for the single-nephron model developed earlier in the chapter. Here, however, we give the details in the text, since they are somewhat more complicated. Our discussion here is limited to the concentrating mode (ADH present), in which the distal tubule and collecting duct are freely permeable to water but not, according to our assumptions, to  $Na^+$ . The water that is reabsorbed from the collecting duct affects the concentration profile of the interstitium, and it is this effect that we want to take into account.

The distal convoluted tubules of several nephrons typically enter into a common collecting duct, and we shall make the assumption here that the interacting nephrons (of different loop lengths) that were considered above all share a single collecting duct. (It would not change the theory in any substantive way if the collecting ducts were separate, but it would change the notation and setup of the equations.) Note that this single collecting duct runs parallel to the tubules of the multiple loops of Henle of our model, that it shares the interstitium with them, and that it traverses the complete interstitium and therefore, in our notation, extends from  $x = 0$  to  $x = L_{\max}$ .

As was done earlier in this chapter, we use the subscript 3 to denote the collecting duct. The inflow to the collecting duct comes from the distal convoluted tubules of the different nephrons. Recall the assumption made earlier that in the concentrating mode, enough water is withdrawn from the distal convoluted tubule to make the concentration of  $Na^+$  in it equal to  $c_0$  at its distal end, where it joins the collecting duct. Another assumption

made earlier is that the distal convoluted tubule is impermeable to  $\text{Na}^+$ , so that the net rate at which  $\text{Na}^+$  enters this tubule is equal to the net rate at which it leaves (since we assume steady-state conditions). These considerations lead to the equation

$$c^* \int_0^{L_{\max}} Q_1(L, L) \rho(L) dL = c_0 Q_3(0). \quad (4.7.20)$$

The left-hand side of this equation is the sum (integral) of the rate at which  $\text{Na}^+$  is leaving all of the ascending limbs of all of the different loops of Henle (of various lengths  $L$ ), and hence entering the distal convoluted tubules. Recall that  $c^*$  is the  $\text{Na}^+$  concentration at the top of each of the ascending limbs; this is the result of the operation of the juxtaglomerular apparatus. Also, recall that  $Q_1(L, L)$  is the flow rate of water all along the ascending limb of a loop of length  $L$ , and that  $\rho(L) dL$  is the number of loops with length between  $L$  and  $L + dL$ . The right-hand side, of course, is the rate at which  $\text{Na}^+$  enters the collecting duct.

The equations for flow of  $\text{Na}^+$  and water along the collecting duct are similar to those of the descending limb of the loops of Henle, equations (4.7.3)–(4.7.4):

$$\frac{d}{dx} Q_3(x) + (f_{\text{H}_2\text{O}})_3(x) = 0, \quad (4.7.21)$$

$$\frac{d}{dx} (Q_3(x)c(x)) = 0. \quad (4.7.22)$$

Note that we use ordinary derivatives here because the functions in question depend only on the single variable  $x$ .

Finally, we have to modify equation (4.7.6) to take into account the flow of water out of the collecting duct. This water, like the water that flows out of the descending limbs of the various loops of Henle, has to be picked up by the peritubular capillaries. The revised version of equation (4.7.6) is as follows:

$$c(x) \int_x^{L_{\max}} (f_{\text{H}_2\text{O}})_1(x, L) \rho(L) dL + c(x)(f_{\text{H}_2\text{O}})_3(x) = f_{\text{Na}}^* \int_x^{L_{\max}} \rho(L) dL. \quad (4.7.23)$$

The new feature is the second term on the left-hand side,  $c(x)(f_{\text{H}_2\text{O}})_3(x)$ , which represents the amount of  $\text{Na}^+$  picked up by the water that has left the collecting duct as that water flows through the interstitium on its way to being reabsorbed by the peritubular capillaries.

In summary, the equations of the improved model are equations (4.7.2)–(4.7.5) and equations (4.7.20)–(4.7.23). The improved model can be reduced to an integral equation for the unknown interstitial  $\text{Na}^+$  concentration profile  $c(x)$  in much the same way as was done above for the model that neglected the influence of the collecting duct. Much of the work has already been done. The new part is as follows:

First, we use equations (4.7.20)–(4.7.22) to express  $(f_{\text{H}_2\text{O}})_3(x)$  in terms of  $c(x)$ . We have

$$Q_3(x)c(x) = Q_3(0)c_0 = c^* \int_0^{L_{\max}} Q_1(L, L) \rho(L) dL, \quad (4.7.24)$$

and hence

$$Q_3(x) = \frac{c^*}{c(x)} \int_0^{L_{\max}} Q_1(L, L) \rho(L) dL. \quad (4.7.25)$$

Therefore,

$$(f_{\text{H}_2\text{O}})_3(x) = -\frac{dQ_3}{dx} = \frac{c^*}{(c(x))^2} \frac{dc}{dx} \int_0^{L_{\max}} Q_1(L, L) \rho(L) dL. \quad (4.7.26)$$

Substituting into this the expression for  $Q_1(L, L)$  derived above (equation (4.7.7)), and then substituting the result into equation (4.7.23), we obtain

$$\begin{aligned} \frac{1}{c(x)} \frac{dc}{dx} (x) \left( \int_x^{L_{\max}} \frac{L \rho(L) dL}{1 - c^*/c(L)} + \int_0^{L_{\max}} \frac{(c^*/c(L)) L \rho(L) dL}{1 - c^*/c(L)} \right) \\ = \int_x^{L_{\max}} \rho(L) dL, \end{aligned} \quad (4.7.27)$$

which should be compared to equation (4.7.11). Note that the new term is an integral from 0 to  $L_{\max}$ , not  $x$  to  $L_{\max}$ . The reason for this is that the collecting duct receives fluid from loops of all lengths. Manipulating this exactly as we did equation (4.7.11), we arrive at

$$c(X) = c_0 \exp \left( \int_0^X \frac{\int_x^{L_{\max}} \rho(L) dL}{\int_x^{L_{\max}} \frac{L \rho(L) dL}{1 - c^*/c(L)} + \int_0^{L_{\max}} \frac{(c^*/c(L)) L \rho(L) dL}{1 - c^*/c(L)}} dx \right), \quad (4.7.28)$$

which is the improved version of equation (4.7.13). (Again note the different limits on the two integrals in the denominator.) Like equation (4.7.13), this is an integral equation for the unknown function  $c(x)$ , which appears on the left-hand side as  $c(X)$  and on the right-hand side as  $c(L)$ . A suggested computing project will be the numerical solution of these two integral equations, to compare their solutions. Note that in the limit  $c^* \rightarrow 0$ , equation (4.7.28) reduces to the same explicit formula for  $c(X)$  as is obtained by taking that same limit in equation (4.7.13), namely, equation (4.7.14). This means that as  $c^* \rightarrow 0$ , the presence of the collecting duct has less and less influence on the concentration profile of interstitial solute. (The same phenomenon happens in a single-nephron model; see Exercise 4.7.) Think about why this is the case!

collecting duct when ADH is present. Recall that we made the approximation that the latter flow is small in comparison with the former.

4.7. A More Complete Model

How are the equations of the single-nephron model changed when the flow of water out of the collecting duct is not neglected? (Hint: This water has to be picked up by the peritubular capillaries.)

Solve the equations of this more accurate model under the assumption that  $c^*$  is given and compare the results with those of Section 4.5. In particular, show that

1. The interstitial fluid is slightly more *dilute* when the kidney is in the concentrating mode than when it is in the diluting mode.

2. The approximation of neglecting the flux of water out of the collecting ducts gets better and better as  $c^*/c(0) \rightarrow 0$ .

4.8. Influence of the Loop-Length Distribution on the Solute Concentration That an Interacting Nephron Population Can Achieve

This exercise relates to the section at the end of the chapter, in which we considered a population of nephrons of different lengths interacting through their shared interstitium. Make the approximation  $c^* = 0$  and therefore use equation (4.7.14), which is an explicit formula for  $c(X)$ . In the text we evaluated this formula for the special case  $\rho(L) = \text{constant}$ , independent of  $L$ , which implies a uniform distribution of loop lengths. Now consider a more general case given by  $\rho(L) = a(L_{\max} - L)^p$ , where  $a$  is an arbitrary constant (which should not affect your result: do you see why?), and  $p$  is a positive (but possibly fractional) power. The point of the problem is to see how the power  $p$  affects the concentrating ability of the nephron population. Therefore, evaluate  $c(X)$  in terms of  $p$ , paying particular attention to  $c(L_{\max})$ . Make a table or graph showing how  $c(L_{\max})/c_0$  depends on  $p$ . Take the limit  $p \rightarrow 0$  to check that you recover the result found in the text. Hint: It will help in evaluating the integrals to make a change of variables such as  $Z = L_{\max} - L$ .