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Renal Physiological Engineering – Optimization Aspects

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1. Introduction

Renal overall functional performance is characterized by excretory function of major end products of protein metabolism, regulation of ionic processes, maintenance of fluid balance and blood volume regulation. Minor functions include hormonal regulation of red cell production and stabilization of blood pressure. Although the kidneys comprise less than 0.5% of total body weight, they receive approximately 20% of the total cardiac output [1]. This consideration underscore the important role played by the kidneys.

The renal circulation has a unique sequence of vascular elements: a high-resistance afferent arteriole, a high-pressure glomerular filtration capillary structure, another high-resistance efferent arteriole and a series of tubular structures with unique absorption/excretion properties. The basic functional unit is the nephron. The nephron consists of a glomerular filtration structure and a tubular system, with its associated vascular elements.

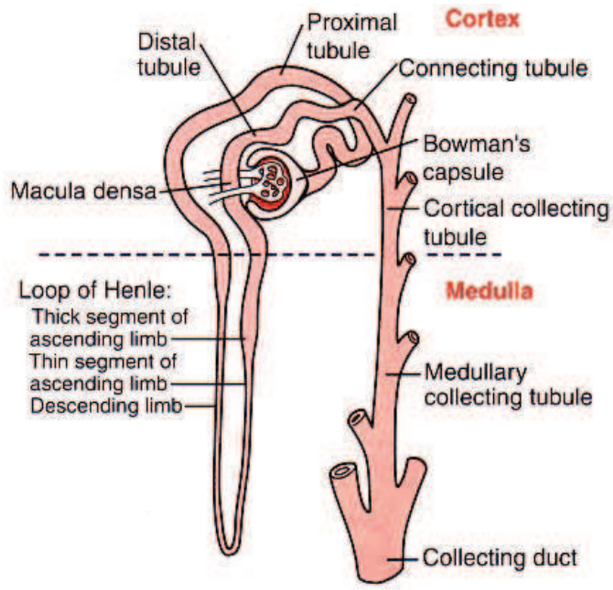


Fig. 1. Diagram of a nephron unit (adapted from [1]).

Structurally, there are 500,000 – 1,000,000 nephron units in the kidney [1,2]. Each nephron has a length of 40 mm and tubular diameter of 50 um. Microscopic puncture and perfusion techniques make it possible to measure single-nephron filtration rates, absorption and secretion rates. The single-nephron glomerular filtration rate (SNGFR) is approximately 30 nl/min.

Approximately 1200 ml/min of blood flow to the kidneys which represents 20% of total cardiac output. In the filtration mechanism, a total filtration surface of 1 m^2 is found. A global renal fitrate of 120 ml/min (180 L/day) is produced by both kidneys, of which 99.4% of water is reabsorbed to yield about 1 liter of urine/day. The concentration ability of the renal system is largely resides in the tubular system embedded within the renal medulla. Figure 1 demonstrates the disparate functionality of the renal nephron unit.

In this paper we will analyse the operating characteristics of the renal system and examine the optimal features of several aspects of renal physiological engineering mechanisms, particularly, the countercurrent multiplier mechanism for urine concentration and how optimal renal function in terms of renal clearance is maintained.

2. Kidney functional analysis

2.1 Countercurrent mechanisms and modelling of urine concentration

The concentration ability of the kidney is provided by a highly hyperosmotic renal medulla, which draws H_2O from the urinary filtrate within the collecting duct. The mechanism for providing and maintaining this highly hyperosmotic environment is found to be due to several mechanisms. The countercurrent multiplier process in the loop of Henle provides one of the most important mechanisms for this purpose. If the renal tubule is straight, it can provide a osmotic gradient within the renal medulla by about 300 mOsm/L, through an active Na^+ transport. However, for this gradient to continue, it requires rapid replacement against washout or dissipation of the osmotic environment in the renal medulla.

By looping the tubule in a parallel configuration and iterating the single effect of concentration, the kidney can generate and maintain the medullary concentration gradient up to 1200-1400 mOsm/L with lower energy costs. The two parallel tubes of the descending limb and the ascending limb of the loop of Henle are looped in close proximity in the hair-pin configuration (figure 1). The production of a chemical osmotic gradient is based on the active sodium reabsorption (requiring ATP) from the ascending loop; the maintenance of this gradient is crucial. The osmolality of interstitium in almost all parts of the body is about 300 mOsm/L. However, in the renal interstitium, the countercurrent mechanism provides increases up to 4 times from 300 mOsm/L to almost 1400 mOsm/L.

The hyperosmotic gradient provides the osmotic pressure to draw passive diffusion of water from the descending limb and the collecting duct. The countercurrent parallel design allows the descending limb to feedback to the ascending limb, forming a closed stable system of hyperosmolar environment and gradient, as shown in figure 2. It is the preservation of this hyperosmolar environment in steady state conditions that allows the urinary filtrate to be concentrated rapidly and efficiently.

There is also a parallel system of renal vascular network of the vasa recta to prevent this hyperosmolar environment from dissipation. The contribution of the vasa recta into the concentrating mechanism is shown as follows: assume the interstitial tissue of cortex and glomerular filtrate are iso-osmotic to plasma. The tubular fluid entering the descending loop of Henle is also iso-osmotic to plasma. This fluid becomes progressively concentrated towards the bend. In the ascending loop it becomes less concentrated as it reaches the cortex. Under the influence of anti-diuretic hormone, blood flow through the vasa recta is

decreased and osmotic equilibration of blood in the vasa with medullary interstitium is enhanced. In brief, the anatomical configuration of the vasa recta minimises but does not prevent solute loss from the medulla via the blood.

Other mechanisms in concentration include the role of urea re-circulated from the collecting duct, the role of vasopressin (antidiuretic hormone or ADH) acting on water transport cellular membrane water channel proteins aquasporin 1, 2, 3 and 4 regulating water permeability. Mutations of several aquasporin genes lead to loss of function and marked abnormalities of water balance, as documented in several reports involving AQP1 knock-out animals.

The contribution of urea to the concentration gradient in the renal medulla is also an important consideration. Diffusion of H_2O occurs from the tubular lumen into the interstitium. Active transport of Na^+ occurs from the tubular fluid. The withdrawal of H_2O from the collecting tubule leads to increased concentration of urea in the collecting tubule, causing a high gradient across the duct membrane, which favours diffusion of urea from the collecting duct into the medulla. From there, the urea diffuses into the descending loop of Henle and is re-circulated into the collecting duct. This contributes to the high urea content and osmolality of the medulla in the concentrating kidney.

2.1.1 Counter-current multiplier mechanism in the loop of Henle

The countercurrent mechanism in the loop of Henle is illustrated in figure 2:

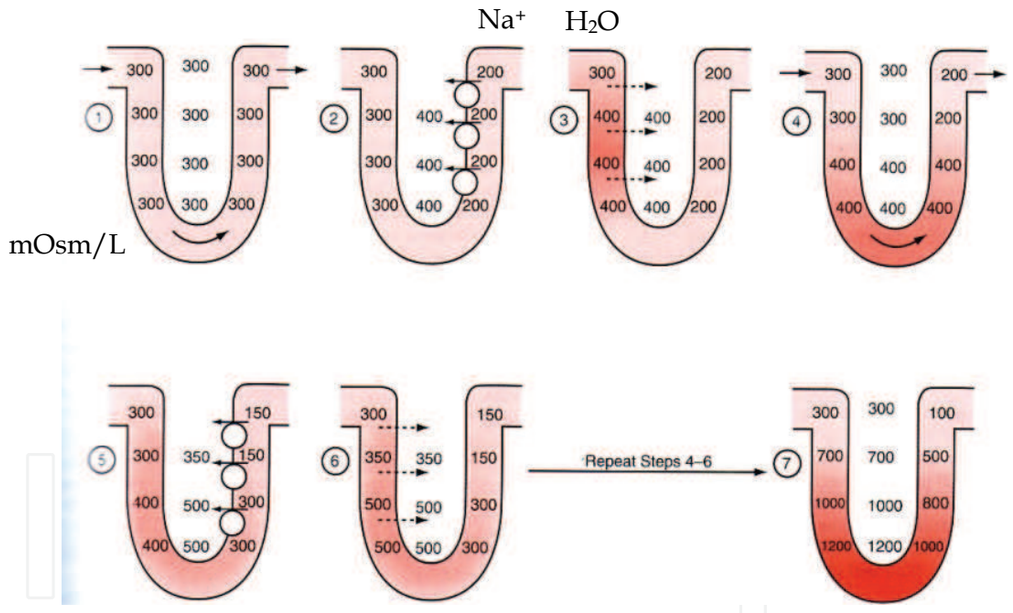


Fig. 2. Countercurrent multiplier process in the loop of Henle, in creating osmotic gradient and urine concentration (adapted from [1]). Note Na^+ absorption from the ascending limb, and passive diffusion of H_2O from the descending limb.

For the loop of Henle shown in figure 2, as a start, it is assumed that the loop of Henle is filled with a fluid with a concentration of 300 mOsm/L. First, the sodium transport from the lumen of the ascending limb to the interstitium, which instantaneously equilibrates with the descending limb. The osmolality in the ascending limb decreases. Because of the higher osmolar interstitium, the fluid in the descending limb increases in osmolality as water is shifted out by passive osmosis. However, the hair-pin structure causes the flow of hyperosmolar fluid in the descending limb to enter the ascending limb. The steps are

repeated over and over, with the effect that the process gradually traps sodium in the medulla and multiplies the concentration gradient until the osmolality of the fluid in the loop of Henle and the interstitium reaches 1200 to 1400 mOsm/L.

2.1.2 Concentration of urine in the medullary interstitium

As discussed, tubular fluid entering descending loop of Henle is iso-osmotic to plasma. This tubular fluid becomes progressively concentrated towards the bend. In the ascending loop, it becomes less concentrated as it rises to the cortex (decreasing from over 1000 to 100).

Within the medullary interstitium, other mechanisms co-operate to concentrate the urine. Under the influence of ADH (anti-diuretic hormone) blood flow through the vasa recta is decreased, and osmotic equilibration of blood in the vasa recta with medullary interstitium is enhanced. Solutes such as sodium, chloride and urea enter the descending blood vessels as they pass through the progressively higher osmolality of the interstitium and H_2O leaves the vessels. In the ascending limb, the opposite events take place and H_2O is reabsorbed into the blood vessels.

In brief, the anatomical configuration of the vasa recta minimises but does not prevent solute loss from the medulla via the blood supply. Because of diffusion of H_2O from the tubular lumen into the interstitium, there is equilibrium between fluid in the collecting tubule and that in the interstitium. The withdrawal of H_2O from the collecting tubule leads to increase in the concentration of urea in the collecting tubule causing a high gradient across the duct membrane, which favours diffusion of urea from the collecting duct into the interstitium. From there, urea diffuses into the descending limb of the loop of Henle and is recirculated into the ascending limb and back into the collecting duct, contributing to the high urea concentration in the medulla in the concentrating kidney.

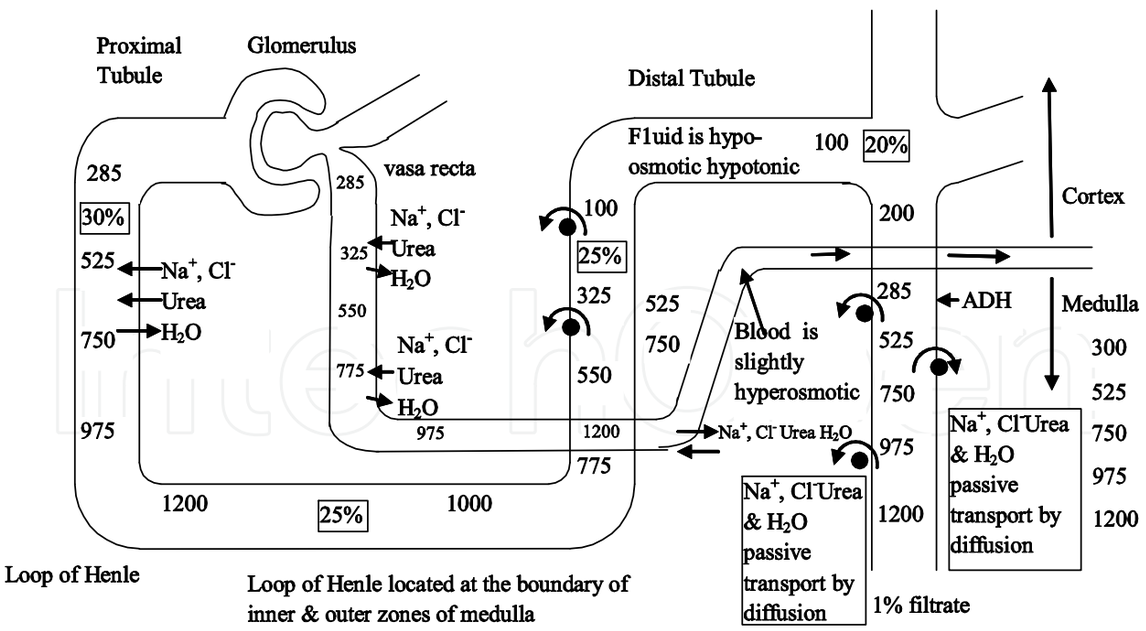


Fig. 3. Schematic diagram showing both the countercurrent multiplier process in the loop of Henle and the vasa recta producing the osmotic gradient. Depicted in the figure are: (i) the passive and active exchanges of water and ions, (ii) concentrations of tubular urine and peritubular fluid in millimetres per litre, (iii) percentages of glomerular filtrate within the tubule at various levels.

In summary (please refer to figure 3),

1. In descending limb, Na^+ transports passively, Cl^- follows and H_2O transport by osmosis because the medullary region is hyperosmotic.
2. In ascending limb, Na^+ transports actively, Cl^- follows.
3. In distal tubule and collecting duct, presence of ADH makes water flow out osmotically (therefore the urine becomes very concentrated).

2.1.3 Linear coupled system of the loop of Henle and analytical solutions

In this model, the driving force for increasing the osmolality (largely contributed by the concentration of Na^+) of the descending limb is proportional to the difference in the osmotic gradient between it and renal interstitium. The renal interstitium itself has a osmotic concentration proportional to the ascending limb of the loop of Henle, due to active transport of Na^+ out of the ascending limb.

The osmolality (largely due to the concentration of Na^+) of the ascending limb is modelled on active sodium transport and hence the rate of fall is only related to its own concentration/osmolality.

The concentration of the interstitium is largely identical to the concentration in the descending tubule as there is passive movement of water through the descending tubule.

The schematic figure 4 illustrates the model of the renal tubule.

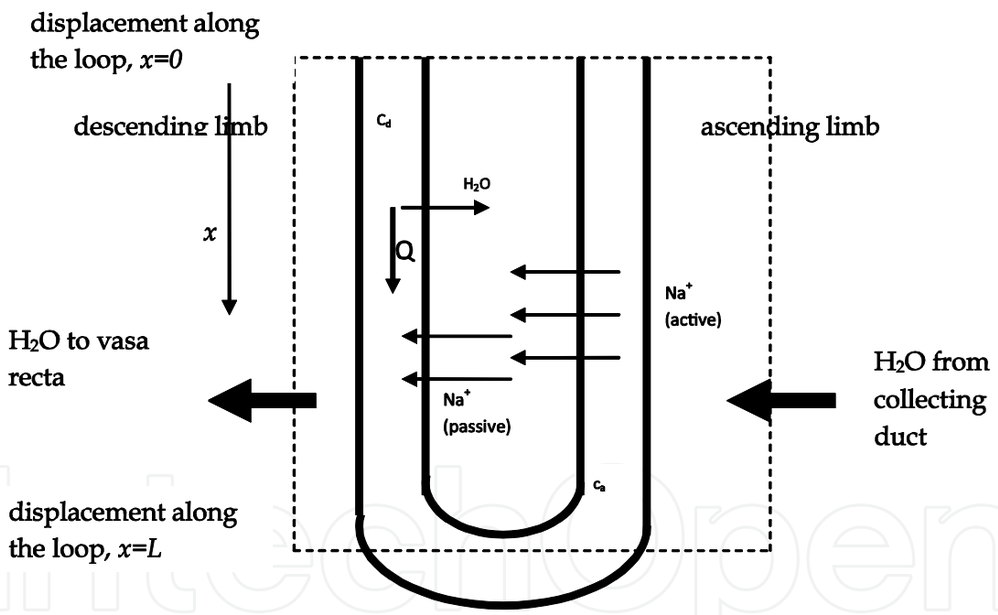


Fig. 4. Schematic diagram of the loop of Henle.

x the distance along the loop of Henle measured from the origin of the descending limb (in mm)

L the total actual length of the loop of Henle measured along one of the limb (in mm)

C_d the concentration of Na^+ in the descending limb (in mOsm/L)

C_a the concentration of Na^+ in the ascending limb (in mOsm/L)

C_i the concentration of Na^+ in the interstitium (assumed proportional to C_a i.e $= k_0 C_a$) (in mOsm/L)

k_d the transport coefficient of Na^+ ions into the descending limb (in ml/min.mm)

k_a the active transport coefficient of Na^+ out of the ascending limb due to Na^+ pump

Q is the tubular flow rate, assumed to be fairly constant in the first approximation (in mL/min)

The governing equations for the descending and ascending limbs of the loop of Henle are shown as a coupled system of linear first-order ODEs, with C_d and C_a the concentration/osmolality of the descending and ascending limbs of the loop of Henle respectively. In the descending limb, the change of concentration of Na^+ is modelled as proportional to the concentration difference between the interstitium and the descending limb. In the ascending limb, the change of concentration of Na^+ is modelled as directly proportional to the concentration in the ascending limb itself through active removal of Na^+ by the Na^+ pump. This leads to the following linear coupled system:

Na+ in the descending limb:
$$\begin{aligned} \frac{d(QC_d)}{dx} &= k_d(C_i - C_d) = k_d k_0 C_a - k_d C_d \\ \frac{dC_d}{dx} &= \frac{k_d}{Q}(C_i - C_d) = \frac{k_d k_0}{Q} C_a - \frac{k_d}{Q} C_d \end{aligned} \tag{1}$$

Na^+ in the ascending limb:
$$Q\frac{dC_a}{dx} = k_a C_a \tag{2}$$

with $k_d, k_a > 0$. The flow rate Q in the renal tubule is taken as constant in the first approximation. Expressed as matrix equation with upper triangular matrix,

$$\begin{pmatrix} C_d' \\ C_a' \end{pmatrix} = \begin{pmatrix} -\frac{k_d}{Q} & \frac{k_d k_0}{Q} \\ 0 & \frac{k_a}{Q} \end{pmatrix} \begin{pmatrix} C_d \\ C_a \end{pmatrix} \tag{3}$$

The eigenvalues are $-\frac{k_d}{Q}$ and $\frac{k_a}{Q}$ and the eigenvectors are $\begin{bmatrix} 1 \\ 0 \end{bmatrix}$ and $\begin{bmatrix} k_d k_0 \\ k_d + k_a \end{bmatrix}$. The general solution of this system is given by:

$$\begin{pmatrix} C_d \\ C_a \end{pmatrix} = H_1 \begin{bmatrix} 1 \\ 0 \end{bmatrix} e^{-\frac{k_d}{Q}x} + H_2 \begin{bmatrix} k_d k_0 \\ k_d + k_a \end{bmatrix} e^{\frac{k_a}{Q}x} \tag{4}$$

where H_1 and H_2 are constants of the solution.

Analytically in phase space, since the 2 eigenvalues are real and opposite in sign, the origin of the linear system is a saddle point, asymptotically unstable. Hence, it is unlikely that the system will remain in the state of zero concentration in the ascending and descending limbs. In fact, the solution (4) shows that the system will tend towards a state where an increasing concentration exists in the loop of Henle, because of the positive eigenvalue k_a / Q (representing active sodium transport in the ascending limb) for large x. This is consistent with the observation that it is the active sodium transport in the ascending limb that drives the production of the concentration gradient within the interstitium of the renal medulla and keeps the countercurrent mechanism operational, rather than the passive osmotic gradient as governed by $-k_d / Q$ which tends to dissipate the osmotic gradient.

At the loop end of the loop of Henle, the concentration/osmolality can reach extremely high levels, driven by active sodium transport. Indeed if the active Na^+ transport $k_a = 0$, then the

system decays to a baseline value through the exponential term associated with k_d. This shows that without active transport, the concentration gradient and the countercurrent multiplier mechanism will dissipate within the renal medulla.
If we take the boundary conditions provided by empirical data in figure 2:

$$C_d(0) = 300 \text{ mOsm/L}$$

$$C_a(0) = 100 \text{ mOsm/L}$$

and assuming trial values of $\frac{k_d}{Q} = \frac{k_a}{Q} = 1/\text{mm}$, the concentration within the ascending and descending limbs are obtained as:

$$C_d = 250e^{-x} + 50e^{x}$$
$$C_a = 100e^{x}$$

This is plotted in the following figures:

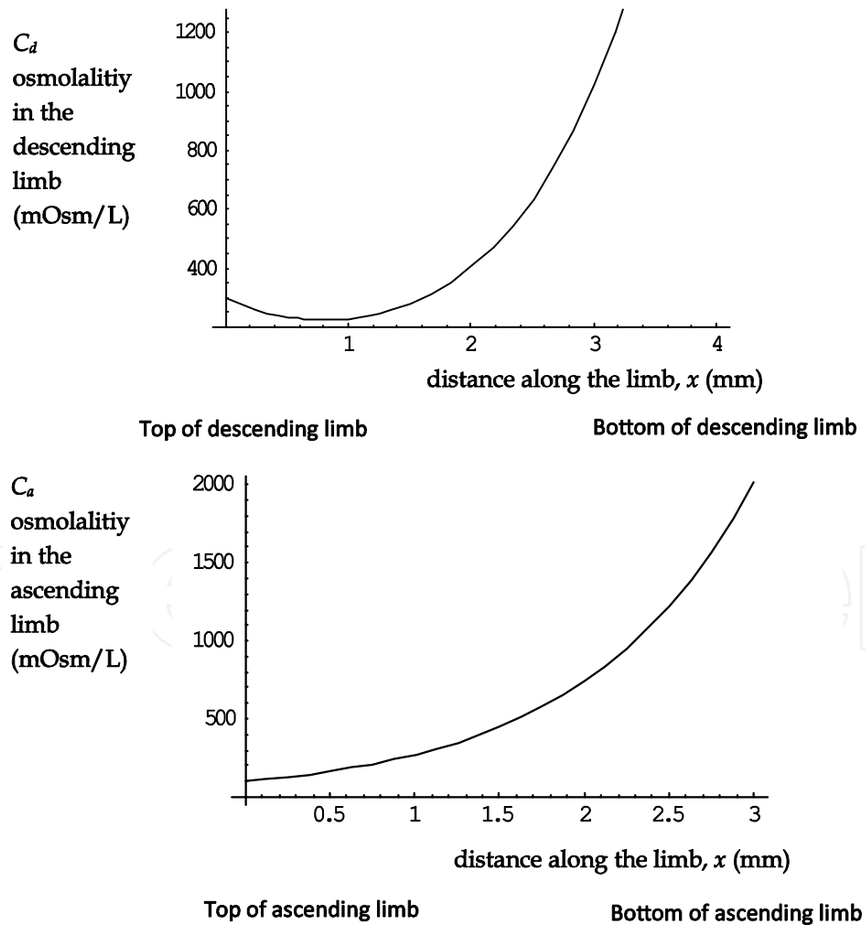


Fig. 5. Variation of Fluid Osmolality in the Descending and Ascending limbs of the Loop of Henle.

Although the values of kinetic transport coefficients are trial values, we can see how the model predicts the shape of the osmolality profile within the descending and ascending loops. The graphical representations in figure 5 demonstrate the highest level of osmolality achieved at the bottom end of the loop is about 1500 mOsm/L, reasonably consistent with empirical data. This model provides analytical solutions beyond that of Keener and Sneyd [3].

The limitations of this model is in the assumption of the values of transport coefficients of the descending and ascending tubules in the appropriate units, its linearity assumption and the disregard of its interaction with other modes or mechanisms of osmotic concentration. However, it can be seen that the analytical solutions provide a reasonable qualitative profile of the urinary concentration within the loop of Henle, under the assumptions made of its properties of its different segments and its "iterative" or "multiplier optimal design".

2.2 Single compartmental model of renal clearance kinetics – (1) single input

One of the important function of the kidney is excretion of metabolic waste products. How the kidney handles this excretory function has direct implications on clinical or physiological function. It is thus of interest to analyse the behaviour of the kidney as an excretory system.

Most accessible to analysis is the renal response to a single bolus of a metabolic substrate. Most renal clearance kinetics analyse the behaviour of the excretory function of the kidney in respect to endogenous or exogenous substrates. In some assessments, it involves the administration of a single bolus dose of an exogeneous substance into the blood circulation.

When a single bolus of such a substance is introduced into the human body system though an intravenous injection, the substance will initially spread out in the circulatory system and distribute into the extravascular body-fluid compartments of the body, while it is at the same time being removed by the kidney. Hence, if we represent the human body as a two-compartment system, then there will be 2 phases of decrease of the plasma concentration of this substance. The first phase represents the fall due to rapid distribution of the substance within the body from the blood circulation into the equilibrium body fluid compartments of the body, while it is at the same time being removed by the kidney. The second phase represents the fall due largely to the renal excretion of this substance.

However, in most cases, the first phase can be ignored and corrected for by empirical approximation so that only the second slower phase needs to be measured. Hence, a single late exponential function can be used to describe the fall in the plasma concentration of the substance. This principle is used in the physiological measurement of renal clearance or glomerular filtration rate (GFR) in human subjects.

2.2.1 Renal clearance analysis using a single-bolus model of renal tracer or substrate

Assume the amount of the tracer in the entire compartment is A (in mg or mmols). Let the concentration of the tracer in the compartment at time t be C_t (in mg/L or mmol/L) and the clearance be annotated as g (in L/min). By definition, $C = A/V$, where V is the total plasma volume or distribution volume, reasonably assumed constant in the body.

By the principle of mass conservation,

$$\frac{dA}{dt} = -g \cdot C_t \tag{5}$$

This is the governing first-order linear differential equation representing the kinetics of a one-compartment system.
Integrating over all time, the total tracer dose injected (D) is given by:

$$\int_0^\infty \frac{dA}{dt} dt = D = -\int_0^\infty g C_t dt = -g \int_0^\infty C_t dt \tag{6}$$

The absolute magnitude of the renal clearance g is:

$$|g| = \left| \frac{D}{\int_0^\infty C_t dt} \right| = \frac{\text{total dose of tracer injected}}{\text{area under the tracer concentration-time curve}} \tag{7}$$

We can show that the concentration of tracer in this compartment follows an exponential variation, by rewriting equation (5) as:

$$V \frac{dC_t}{dt} = -g \cdot C_t \tag{8}$$

Separating variables, we get:

$$\int_{C_0}^{C_t} \frac{dC_t}{C_t} = -\frac{g}{V} \int_{t_0}^{t} dt$$

We have a mono-exponential clearance scheme, as follows:

$$C_t = C_0 e^{-\frac{g}{V}(t - t_0)} \tag{9}$$

By taking logarithms of both sides, we get a linear relationship on the "semi-log" scale as:

$$\ln C_t = \ln C_0 - \frac{g}{V}(t - t_0) \tag{10}$$

Equation (10) is the basis of plotting the tracer concentration against time as a semi-log graph, so that (i) the absolute value of the gradient of the slope will be given by (renal clearance)/V, which is also called the clearance constant λ, and (ii) the y-intercept will be given by C_0 which is D/V.
So the initial volume of distribution, V, will be given by

$$V = \frac{D}{C_0} \tag{11}$$

Hence,

$$\text{Renal clearance} = V \times \lambda = \frac{D}{C_0} \times \lambda \tag{12}$$

Or, the estimated renal clearance is the

$$\text{Distribution volume} \times \text{Clearance constant} = \frac{\text{total dose injected}}{\left(\text{y-intercept of ln C vs t curve}\right)} \times \left(\text{gradient of ln C vs t curve}\right)$$

Historically, this methodology is often known as the indicator-dilution method or the Stewart-Hamilton method, although the origins of this method antedate the work of Stewart and Hamilton [4,5].

2.2.2 Physiological measurement of the Glomerular Filtration Rate (GFR)

If we can insert a microneedle with a flow gauge into each glomerulus in the kidney and measure the flow rate experimentally, this would constitute one way of measuring the GFR. This can be done in-vitro with micropuncture and microperfusion techniques. On a body system level, the global renal clearance has to be obtained by other ways.

Typically, GFR is deduced by measuring the renal filtered loss or clearance of a suitable substance from the plasma. In physiological tests, creatinine clearance and Cr-51 EDTA clearance are typically used. Dynamic renogram modelling of impulse tracer kinetics through the kidney had previously been performed [6].

In order to measure GFR accurately, the following properties must apply to the particular substance used to measure GFR :

1. the substance must be freely filtered through the glomerulus
2. it must not undergo renal tubular secretion or absorption
3. it must not bind to plasma proteins
4. it must not be lost through any other methods from the body
5. it must not be metabolised or changed chemically in the body.

These are severe restrictions and there are only some possible candidates for this substance, including :

1. endogenous creatinine, but this is less accurate in children
2. inulin
3. chromium-51 EDTA
4. technetium99m-DTPA

If the loss of these substances from the body can be measured, one can get a quantitative reflection of the excretory function of the kidney.

Of the four substances mentioned, only endogenous creatinine is found within the human body. The other substances have to be introduced into the human body. Inulin is a polysaccharide molecule with a molecular weight of 5200. Creatinine itself is a by-product of skeletal muscle metabolism, and it is present in the plasma at a relatively constant concentration and does not require intravenous infusion into the patient. However, creatinine is not a perfect marker for GFR because a small amount of it is secreted by the tubules and hence it is not a pure glomerular agent and tends to overestimate the GFR.

Incidentally, there is an agent, para-aminohippuric acid (PAH), which is not only filtered but also secreted to a large extent, so that it can be used to measure not the GFR but the effective

renal plasma flow rate. Chromium-51 EDTA is a radiolabelled EDTA with the gamma emitter, chromium-51. This agent is very close to a purely glomerular filtered agent. Tc99m-DTPA is also a glomerular filtered substance, radiolabelled to the gamma emitter, Tc99m.

2.2.3 Continuous input of substrate model – relationship between steady-state serum creatinine concentration in the body and renal clearance

2.2.3.1 Theory and application

As opposed to the single-bolus renal kinetics, in the body, endogenous metabolic substrates are introduced into the blood circulation in a continuous way. Thus the model of renal clearance kinetics given above will have to be modified to take this continuous input into account. Analysing this continuous input model will be useful to evaluate the optimal and crucial renal handling of endogenous waste products in a typical human body.

The result of such a continuous input and renal excretion gives rise to a steady-state concentration of a renal-excreted substrate in the body. A typical endogenous substrate produced in a continuous fashion in the body and excreted by the renal route is creatinine. Figure 6 shows an inverse relationship between plasma creatinine concentration and GFR. The lower the renal clearance, the higher is the steady-state blood concentration of the substrate. However, this relationship is not linear but largely inverse rectangular hyperbolic (see figure 6).

To analyse this empirical relationship, further analysis can be performed using the single-compartment model but introducing a continuous input of substrate. This analysis follows from and extends the results obtained by Mazumdar [7].

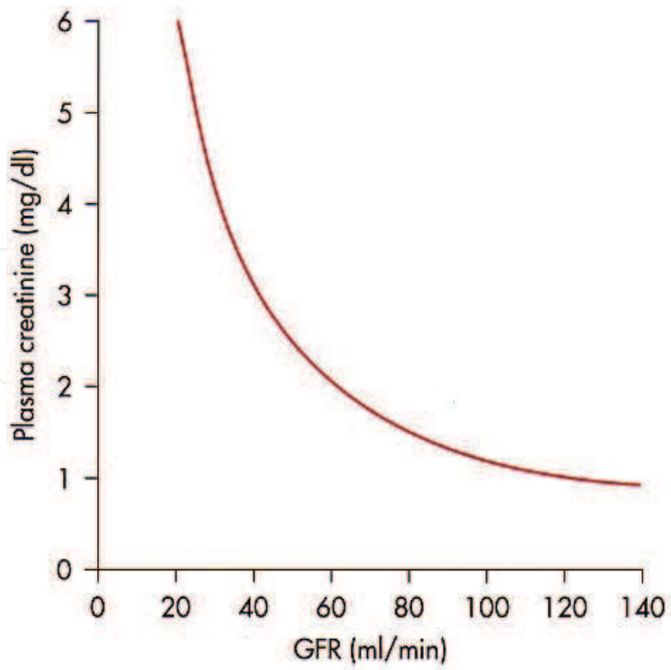


Fig. 6. Empirical relationship between blood creatinine levels and the renal clearance rate (adapted from [2]).

If instead of a single dose of tracer or substrate given as discussed in the previous section, constant doses of creatinine (substrate) are given at equal intervals of time ie, at intervals of period T, then using the single-bolus equation (7), the concentration of the substrate immediately after the second dose is given by:

$$C_1 = C_0 + \left(C_0 e^{-\frac{g}{V}T} \right) \tag{13}$$

Immediately after the third dose, the substrate concentration is given by:

$$\begin{aligned} C_2 &= C_0 + \left[C_0 + \left(C_0 e^{-\frac{g}{V}T} \right) \right] e^{-\frac{g}{V}T} \\ &= C_0 + C_0 e^{-\frac{g}{V}T} + C_0 e^{-\frac{2g}{V}T} \end{aligned} \tag{14}$$

Immediately after the nth dose, the substrate concentration is given by:

$$\begin{aligned} C_{n-1} &= C_0 + C_0 e^{-\frac{g}{V}T} + \ldots + C_0 e^{-(n-1)\frac{g}{V}T} \\ &= C_0 \left[1 + e^{-\frac{g}{V}T} + \ldots + e^{-(n-1)\frac{g}{V}T} \right] \\ &= C_0 \frac{1 - e^{-n\frac{g}{V}T}}{1 - e^{-\frac{g}{V}T}} \end{aligned} \tag{15}$$

As n tends to infinity, the creatinine concentration approaches an equilibrium value, given by:

$$C_\infty = \frac{C_0}{1 - e^{-\frac{g}{V}T}} \tag{16}$$

Linearization by Taylor's series approximation gives the equilibrium concentration of the creatinine in the blood to first order, as:

$$C_\infty = \frac{C_0}{\frac{g}{V}T - \frac{1}{2}\left(\frac{g}{V}T \right)^2 + \ldots} \approx \frac{(C_0 / T)V}{g} \tag{17}$$

where $(C_0 / T)V$ is the amount of the creatinine introduced per unit time. Hence, using the parameter values in Table 1,

$$C_\infty \approx \frac{\text{amount of renal substrate introduced per unit time}}{\text{renal clearance}} = \frac{10.1}{\text{renal clearance}} \tag{18}$$

C_∞ is the steady-state concentration of creatinine, as it is produced and excreted continuously in the body. The relationship derived is the equilibrium or steady-state concentration of the substrate that is produced continuously in the body and excreted renally. The relationship is plotted in figure 6.

Rate of body production of creatinine metabolite, *A*	20-25 mg/kg body weight per day (approximately 1.5 g/day in a 70 kg man). In SI units, this would be 10.1 umol/min.
Human body renal clearance, *g*	120 ml/min (approximate).
Total volume of distribution of creatinine in a typical human of weight 70 kg	50,000 ml (approximate)

Table 1. Important physiological renal parameters (data from [2]).

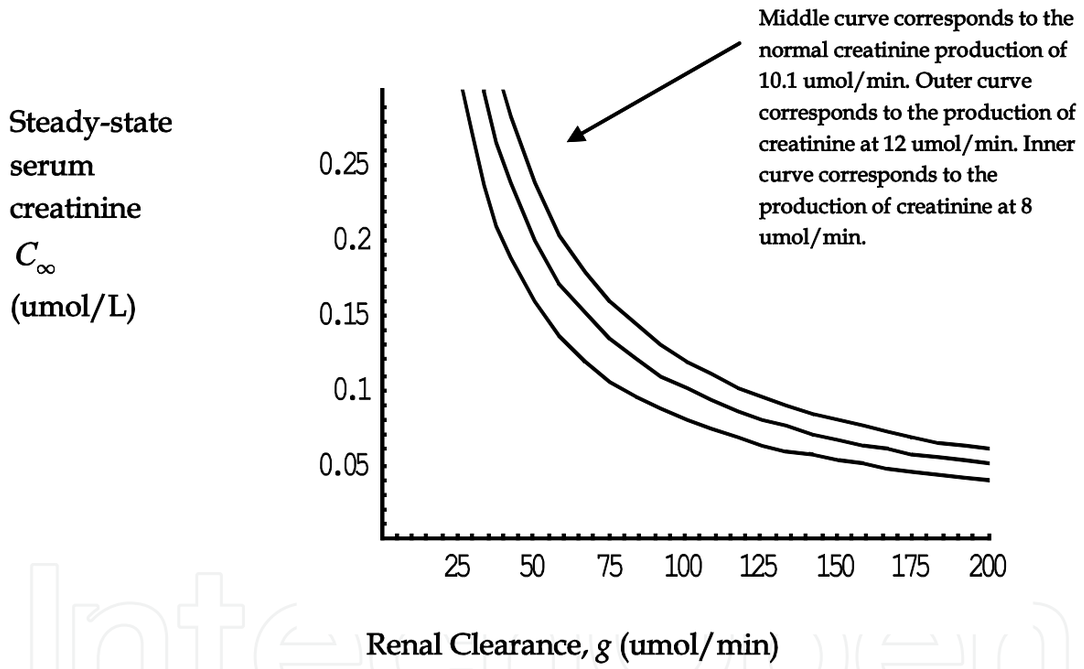


Fig. 7. Model prediction of the relationship between blood creatinine levels and the renal clearance rate.

Graphically, equation (17) predicts a very close approximation to the empirical curve, which is an inverse rectangular hyperbolic relationship between serum creatinine levels and the renal clearance as shown in figure 7.

Depending on the rate of production of the metabolite creatinine in the human body, equation (17) also demonstrates that there is a series of iso-dose curves of renal clearance vs blood levels of renal substrate, similar to isothermal curves in ideal gas thermodynamics.

The application to human physiology can be seen as follows. It is well known that the serum creatinine levels in women is lower than in man. A typical muscular man producing a larger quantity of creatinine substrate due to muscle breakdown will, for the same renal clearance,

demonstrate a higher blood concentration of creatinine for the same degree of renal clearance.

2.3 Renal clearance – convolution analysis

In general, the total amount of substrate in the body at time *t* is given by the convolution of the amount produced by the body per unit time, *A(t)*, which is a function of time and the biological clearance of that substance. In the case of pure renally-excreted substrate, such as creatinine, assuming a single-compartment clearance-kinetics as previously discussed, we have as follows:

Total amount of substrate in the body at time *t*: $A(t) * e^{-\frac{g}{V}t}$ (19)

If as above, the amount of substrate introduced into the blood compartment per unit time is constant, *A*, then the total amount of substrate at time *t* (accounting for renal clearance) is given by:

Total amount of substrate in the body at time *t*: $A * e^{-\frac{g}{V}t} = \int_0^t A du \cdot e^{-\frac{g}{V}(t-u)}$ (20)

The result takes a useful form for physical interpretation. Total amount of substrate in the body at time t is given by:

$$A * e^{-\frac{g}{V}t} = \int_0^t A du \cdot e^{-\frac{g}{V}(t-u)} = \frac{AV}{g}\left(1 - e^{-\frac{g}{V}t}\right) \quad (21)$$

Schematically, this relation is shown in figure 8, for blood creatinine levels:

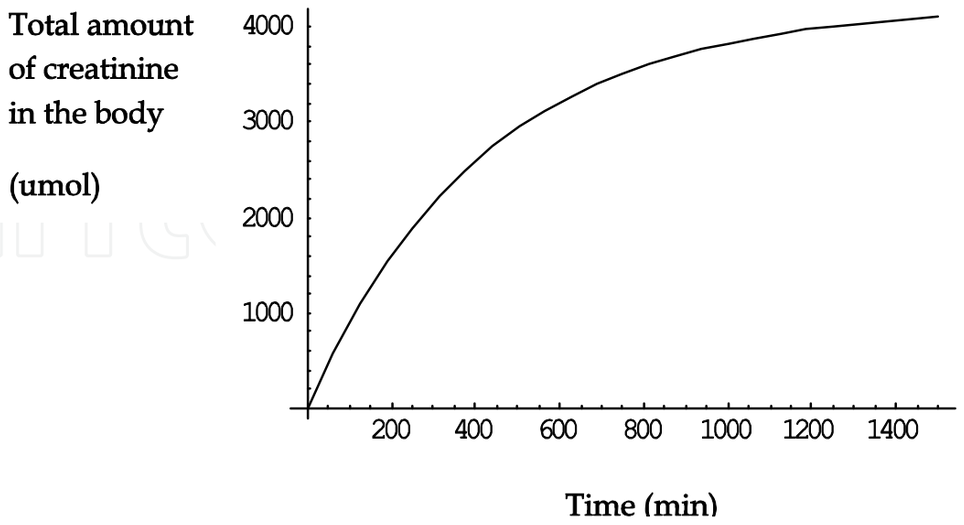


Fig. 8. Asymptotic steady-state concentration of blood creatinine levels, based on convolution analysis.

At $t \to \infty$, the equilibrium concentration of substrate in the blood compartment is:

$$C_{\infty} = \frac{1}{V}\left(\frac{AV}{g}\right) = \frac{\text{amount of substrate introduced per unit time}}{\text{renal clearance}} \tag{22}$$

consistent with the previous equation (18).
Application of the formula can be done using the physiological values in Table 1.
The body produces creatinine at the rate of 20-25 mg/kg body weight per day, which is approximately 1.5 g/day in a 70 kg man. In SI units, this is 10.1 umol/min. The renal clearance is approximately 120 ml/min. Hence, based on equation (22), the estimated steady-state serum creatinine level in the body based on the model would be predicted to be in the order of

10.1/120 = 0.084 umol/ml or 84 umol/L, as expected empirically.

Direct correlation with physiological parameters shows this convolution analysis to give reasonably close results.

3. Conclusion

The analytical model of the loop of Henle and the renal handling of metabolic substrates is aimed at showing to some extent how the renal system is optimized for filtration and regulation of urine concentration by the countercurrent mechanism in the loop of Henle and its medullary environment, which is largely physiologically engineered to increase and maintain at steady-state the high osmolality of the urine fluid to as high as 4 times normal blood osmolality.
The renal clearance of substrates is modelled as a single-compartment kinetic model, with single-input and more physiologically as continuous-input. The analytical solutions obtained from the continuous input of creatinine predict the body creatinine level to tend to asymptotically steady-state substrate blood concentration with time, in a relationship that is an inverse rectangular hyperbolic function to the renal clearance. This is close to the relationship found empirically. The relationship is found to be related to the amount substrate input per unit time divided by renal clearance. The same conclusion is obtained from convolution analysis of renal clearance. The formula predicts reasonable estimates for the actual serum creatinine levels in the body based on renal clearance and substrate input parameters.

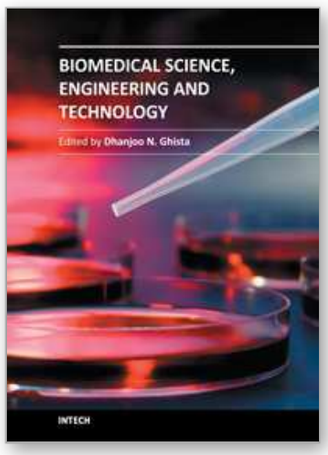
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