Problem Set 7.1
Fluid Volumes, Glomerular Filtration, and Clearance

1. The time course of decay of plasma [inulin] shown in Figure 7.1.1 can be simultaneously used to determine the ECF volume and the GFR. The disappearance of inulin is given by the first-order equation

[7.PS1.1] $$\frac{dN_{inulin}}{dt} = -GFR\ P_{inulin}$$

where N_{inulin} is the number of moles of inulin in the body and P_{inulin} is its plasma concentration. The plasma concentration is the total number of moles of inulin in the body divided by its volume of distribution, the ECF:

[7.PS1.1A] $$P_{inulin} = \frac{N_{inulin}}{ECF}$$

Combining these two equations, we get

[7.PS1.1B] $$\frac{dN_{inulin}}{dt} = -\frac{GFR}{ECF}N_{inulin}$$

This equation describes a first-order decay curve.
   A. Separate variables and integrate the first-order decay equation between the definite limits of time $t = 0$ and t, corresponding to $N_{inulin} = N_0$ and N_t.
   B. Two hours after establishing steady state in a 70-kg person and then stopping infusion, [inulin] falls from the steady-state value of 20 mg% at steady state to 7.2 mg%. Calculate GFR/ECF from the first-order decay equation.
   C. The total urine collected during 8 hours was 500 mL, and the average inulin concentration was 560 mg%. Calculate the ECF.
   D. From B and C, calculate the GFR.
2. A woman weighing 60 kg is given 10 mg of Evan's Blue dye intravenously. Ten minutes later a blood sample was obtained from another vein and colorimetric analysis of the plasma showed 0.4 mg% of the dye. Assume that the administered dye was evenly distributed in the plasma compartment by the end of the 10 minutes and that no dye was lost from the plasma during this period.
   A. Calculate the woman's plasma volume.
   B. If the woman's hematocrit is 0.40, what is her total blood volume?
3. A person has TBW = 42 L and ECF = 14 L and a plasma osmolarity of 300 mOsM. After losing 4 g of NaCl and 2 L in sweat, what is the new ECF and ICF volume and osmolarity?
4. A person has TBW = 50 L and ECF = 16 L and an original osmolarity of 295 mOsM. The person eats a meal that contains 6 g of NaCl and 1 g of KCl and 0.5 L of water. Assume it is all absorbed and distributed. Calculate the estimated new ICF and ECF volume and osmolarity.
5. Suppose you injected someone with deuterated water, ^2H_2O. At some time, the marker water would be evenly distributed among all exchangeable fluid compartments. The ^2H_2O is filtered through the glomerulus, and then reabsorbed. Assume that the total body water is 42 L and ECF is 14 L. The GFR is 120 mL min^{-1} and urine flow is a constant 1 mL min^{-1}. Assume that ingested fluids replenish the urinary losses on a continuous basis.
   A. How long would the ^2H_2O remain in the body? Derive an equation for plasma [^2H_2O] as a function of time.
   B. What would the half-life of ^2H_2O be in the plasma?
   Suppose you inject the same person with inulin and that a peak [inulin] was obtained some minutes later.
   C. Derive an equation for plasma [inulin] as a function of time.
   D. What would the half-life of inulin be in the plasma?
   E. How does this compare to B?
6. A person weighs 105 kg. His total body water is 48 L.
   A. Calculate his lean body mass.
   B. Calculate the percent of body fat in excess of the lean body mass.
   C. Would you say that this person is obese? Why or why not?
7. The empirical fit to the oncotic pressure due to albumin is given by Landis and Pappenheimer (*Handbook of Physiology*, vol. 2, Section 2, pp. 961–1034, 1963) as

[7.PS1.1C] $$\pi_{albumin} = 2.8C + 0.18C^2 + 0.012C^3$$

where $\pi_{albumin}$ is in units of mmHg and C is in units of g% (gram per 100 mL of plasma).
   A. Calculate albumin's contribution to plasma oncotic pressure at the afferent arteriole when [albumin] = 4 g%.

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TABLE 7.PS1.1 Diffusion Coefficients and M_r for a Variety of Proteins

Protein	Molecular Weight	$D \times 10^7$ ($cm^2\ s^{-1}$)	Stokes Radius (a_s)
Milk lipase	6600	14.5	
Metallothionein	9700	12.4	
Cytochrome C	12,000	12.9	
Ribonuclease	12,600	13.1	
Myoglobin	16,890	11.3	
Chymotrypsinogen	23,200	9.5	
Carbonic anhydrase	30,600	10.0	
Peroxidase II	44,050	6.8	
Albumin	68,500	6.1	
Lactoperoxidase	92,620	6.0	
Aldolase	149,100	4.6	

   B. Assume the filtration fraction is 0.2 and that the sieving coefficient for albumin = 0. What is the concentration of albumin at the venule end of the glomerular capillary?
   C. Calculate albumin's contribution to the plasma oncotic pressure at the efferent arteriolar end of the glomerulus.

8. Table 7.PS1.1 lists the diffusion coefficients of a variety of proteins. These were determined in water at 25°C at a viscosity of 1×10^{-3} Pa s, where Pa is pascal = 1 N m^{-2}.
   A. Calculate the Stokes radii for the proteins using the Stokes Einstein equation:

$$D = \frac{kT}{6\pi\eta a_s} \qquad [7.PS1.2]$$

   where D is the diffusion coefficient, k is Boltzmann's constant ($=1.38 \times 10^{-23}$ J mol^{-1} K^{-1}), η is the viscosity, and a_s is the Stokes radius.
   B. Based on these calculations and Figure 7.3.6, what is the approximate molecular weight cutoff of the kidney glomerulus? (This is the molecular weight of a substance corresponding to 50% retention by the membrane.)

9. Given that the average glomerular capillary pressure is about 55 mmHg, plasma oncotic pressure is about 28 mmHg, the hydrostatic pressure within Bowman's space is 20 mmHg, ultrafiltrate oncotic pressure is 0 mmHg, the GFR is 120 mL min^{-1}, and each kidney weighs 125 g, define a filtration coefficient and find its magnitude.

10. The following test results were obtained over a 24-hour period:

Urine volume	=	1.4 L
Urine [inulin]	=	100 mg%
Urine [urea]	=	220 mmol L^{-1}
Urine [PAH]	=	70 mg mL^{-1}
Plasma [inulin]	=	1 mg%
Plasma [urea]	=	5 mmol L^{-1}
Plasma [PAH]	=	0.2 mg mL^{-1}
Hematocrit	=	0.40

    Calculate:
    A. $C_{inulin}, C_{urea}, C_{PAH}$
    B. ERPF
    C. The rate of urea filtration
    D. The rate of urea excretion
    E. The rate of urea reabsorption
    F. The rate of PAH filtration
    G. The rate of PAH excretion
    H. The rate of PAH secretion (assuming no PAH is reabsorbed).

11. The following data were obtained from a research animal:

Urine flow rate	1.5 mL min^{-1}
Urine [inulin]	150 mg%
Plasma [inulin]	1.5 mg%
Urine [A]	18 mg%
Plasma [A]	1.8 mg%
Urine [B]	200 mg%
Plasma [B]	1.0 mg%
Urine [C]	20 mg%
Plasma [C]	0.2 mg%

    A. Based on this information, postulate how the kidney handles substances A, B, and C and justify your answer.
    B. Propose experiment(s) to test your postulates.

12. One model of the glomerular membrane is a microporous membrane in which right cylindrical pores penetrate all the way through the membrane. Assume that the pores have a length of 50 nm and a radius of 3.5 nm. The viscosity of plasma is 0.002 Pa s. The average hydrostatic pressure in the glomerulus is 60 mmHg, hydrostatic pressure in Bowman's space is 20 mmHg, and the average oncotic pressure of glomerular capillary blood is 28 mmHg.
    A. Calculate the flow through a single pore assuming laminar flow (use the Poiseuille flow equation).
    B. How many pores would there have to be to produce a normal GFR?
    C. If the total aggregate area of the kidneys for filtration is 1.5 m^2, what is the density of the pores (the number of pores per unit area)?
    D. What fraction of the area is present as pores?

13. Suppose that the aggregate area of the ultrafiltration surface in the two kidneys combined is 15,000 cm^2 (1.5 m^2). Suppose further that the aggregate area of pores in the glomerular barrier is

5% of the total area. The viscosity of plasma is 0.002 Pa s and the thickness of the barrier is 50 nm. The pressure driving the flow is the balance between the average glomerular pressure at 60 mmHg, the pressure within Bowman's space at 20 mmHg, and the oncotic pressure of plasma at average of 28 mmHg. Assume the rate of filtration is 120 $cm^3\ min^{-1}$.

A. Calculate the average velocity of flow across the membrane.
B. Assuming Poiseuille flow, equate this to the average velocity of flow within the pores, and calculate the equivalent radius of the pores (the radius they would have if they were right cylindrical pores or uniform size).

14. Assume that myoglobin is a spherical protein with a Stokes radius of about 1.9 nm and that the pores in the renal corpuscle have a radius of 3.5 nm.
    A. Give an estimate of σ, the reflection coefficient, for myoglobin. Recall here that if the protein hits the rim, it is assumed to be reflected back into the plasma side of the membrane.
    B. Calculate the sieving coefficient for myoglobin, assuming that the only restriction for myoglobin filtration is at the pore entrance.
    C. In rhabdomyolysis, muscle membranes leak myoglobin into the blood. What do you think happens to that myoglobin, based on your answer to A and B?
15. The following test results were obtained over a 24-hour period:

Urine volume	=	1.2 L
Urine [inulin]	=	110 mg%
Urine [creatinine]	=	170 mg%
Plasma [inulin]	=	0.8 mg%
Plasma [creatinine]	=	1.2 mg%
Hematocrit	=	0.40

    A. Calculate the clearance of inulin.
    B. Calculate the clearance of creatinine.
    C. What is the GFR?
    D. Creatinine is an endogenous by-product of muscle metabolism, originating from creatine. Assuming a steady state, estimate the daily production of creatinine.
    E. If the filtration fraction is 0.18, estimate the effective renal plasma flow.
16. The following test results were obtained over a 24-hour period:

Urine volume	=	1.3 L
Urine [inulin]	=	133 mg%
Urine [glucose]	=	0 mg%
Plasma [inulin]	=	0.8 mg%
Plasma [glucose]	=	90 mg%
Hematocrit	=	0.40

    A. Determine the GFR.
    B. Calculate the clearance of glucose.
    C. Estimate the daily filtered load of glucose. This is how much glucose is filtered per day.
    D. How much glucose is excreted per day?
    E. How much glucose is reabsorbed from the ultrafiltrate, per day?
17. The Stokes radius for water is 0.1 nm; urea's radius is 0.16 nm, and the radii for glucose and sucrose are 0.36 and 0.44 nm, respectively. The radius for inulin, a fructose polymer with a molecular weight of 5.5 kDa, is about 1.6 nm. Assume the radius of the pores in the glomerulus is 3.5 nm. *Hint*: The area available to the solvent is NOT the dimensions of the pore. The reflection coefficient is a parameter of area available to solute relative to water.
    A. Calculate the reflection coefficient for each of the solutes given above, on the assumption that the available area for the solutes is $\pi(a - a_s)^2$, where a is the radius of the pore and a_s is the radius of the solute.
    B. Based on this reasoning, estimate the sieving coefficient, Θ, for these small molecules.
    C. Does your calculation support the idea that inulin is freely filtered? Why or why not?
18. A 60-year-old man is admitted at 5 PM to the hospital after hiking all day and complaining of dizziness. He says he ran out of water the last 5 miles of his hike and the temperature was near 100°F. The patient reports that he last urinated at noon, and his urine was deep yellow. The results of lab tests were:

Na	143 mM
K	5.2 mM
pH	7.38
P_{O_2}	38 mmHg
Cl	102 mM
HCO_3^-	23 mM
P_{CO_2}	97 mmHg
Hemoglobin	15.1 g%
Creatinine	3.1 mg%
Systolic blood pressure	120 mmHg
Diastolic blood pressure	75 mmHg

    A. Which of these variables are abnormal?
    B. Using Eqn (7.4.8), calculate the GFR for this individual. Use $K = 1$. Is this value normal?
    C. Do you think the GFR is low or lower when the patient was admitted?
19. Suppose a person has a GFR of 120 mL min^{-1} and produces creatinine at 1.5 mg min^{-1}. Assume the ECF is 14 L and the rate of secretion is a constant 0.1 mg min^{-1}.
    A. Calculate the steady-state creatinine concentration in plasma.
    B. Suppose that one renal artery experienced a complete blockage and that its contribution to the GFR went to zero, and the total GFR of the body was then 60 mL min^{-1}. Assume also that the secretion of creatinine was halved to 0.05 mg min^{-1}. What would the new steady-state creatinine concentration be?
    C. If the GFR instantaneously changes from 120 mL min^{-1} to 60 mL min^{-1}, and renal secretion is constant but undergoes a step changes from 0.1 to 0.05 mg min^{-1} at the same time the GFR drops, and creatinine

synthesis does not change, derive an equation that describes the time course of the creatinine concentration from its initial steady state to the second steady state. Can this be characterized by a half-life?

20. Alternate pathways for macromolecular ultrafiltration have been considered. Albumin or other substances can get into Bowman's space in several ways: (1) they can diffuse into that compartment across the glomerular filtration barrier; (2) they can be dragged into that compartment by the flow of fluid across the barrier; (3) they can be electrophoresed into the compartment, responding to potential differences between the two compartments. The total flow of albumin is given as

$$Q_A = Q_V(1-\sigma)\overline{C} - D_A A\frac{dC}{dx} - \mu_e \overline{C} A\frac{d\psi}{dx}$$

[7.PS1.1]

where the first term is the flow resulting from solvent drag (where $\overline{C}$ is the average concentration), the second is the flow derived from diffusion, and the third is the flow caused by electrophoresis, where μ_e is the electrophoretic mobility, which depends on the magnitude of charge on the particle, its shape, and the viscosity of the medium. The equation can be written solely in terms of driving forces if we replace

[7.PS1.2] $$Q_V = -L_p A\frac{dP}{dx}$$

where L_p is the hydraulic permeability, A is the area, and P is the pressure that drives fluid flow. Let us suppose that diffusion is the *only* mechanism working to transport albumin across the glomerulus. In the steady state, the input into the aggregate glomerular capillaries must balance the output. The input of albumin is the flow carried by the aggregate afferent arterioles and the output is carried by the efferent arterioles and the ultrafiltrate. This is given as

[7.PS1.3] $$Q_{va}\,C_p = Q_{ve}\,C_g + Q_{vf}\,C_f$$

Here Q_{va} represents the volume flow into the glomerulus from the afferent arterioles, C_p is the concentration of albumin in the incoming plasma, Q_{ve} is the volume flow of plasma out the efferent arterioles, C_g is the average concentration of albumin in the glomerulus, Q_{vf} is the volume flow into the ultrafiltrate, equal to the GFR, and C_f is the concentration of albumin in the ultrafiltrate. Here we view the aggregate of the fluid in the glomerular capillaries as being well mixed, with a single concentration of albumin. Although this is probably not true, it simplifies the problem. The presence of multiple diffusional barriers within the glomerulus makes the diffusion complex. We *define* a permeability, related to the diffusion coefficient within the barriers and the thickness of the barriers, for the entire complex, as

[7.PS1.4] $$p_f = \frac{J_f}{\Delta C} = \frac{Q_{vf}C_f}{A(C_g - C_f)}$$

where C_g is the concentration of albumin within the glomerular capillary. At steady state, the gradient in albumin must be linear.

Given that $Q_{va} = 600$ mL min^{-1}, $C_p = 3.7$ g% = 3.7 g/100 mL; $Q_{ve} = 480$ mL min^{-1}; apparent $\theta = 0.00062$; area of diffusion = 670 cm^2 and thickness of the barrier = 300 nm.

A. Calculate the concentration of protein in the ultrafiltrate from C_p and θ.
B. Given the values for flows and concentrations, calculate the concentration of protein in the glomerular capillaries, C_g.
C. Suppose that the protein that enters the ultrafiltrate does so solely by diffusion and not by solvent drag or electrophoresis. The flow would then be given as

[7.PS1.4] $$Q_A = Q_{Vf}\,C_f = \frac{D_m\,A}{\Delta x}(C_g - C_f)$$

Calculate D_m the diffusion coefficient in the glomerular filtration membrane that would produce the same flow of albumin as is observed.

D. The free diffusion coefficient for albumin in water is 6×10^{-7} cm^2 s^{-1}. Calculate the **hindrance factor**, given as

[7.PS1.5] $$D_m = H_D\,D_W$$

where D_m is the diffusion coefficient in the membrane, H_D is the diffusional hindrance factor (which could differ from the hindrance factor due to filtration), and D_W is the diffusion coefficient in water.