

Computer Simulation of Renal Function Experiments (v. 4.1)
Spring '06, Dr. C. S. Tritt

In this experiment, you'll use a computer simulation of renal function to investigate the operation of the human kidneys. Specifically you'll investigate: a) determinates of RBF, GFR and UF, b) the role of the tubular-glomerular feedback system in the autoregulation of RBF and GFR, c) the relationships between plasma ADH, renin and aldosterone on the excretion of water and electrolytes, d) the relationship between renal neural activity and the excretion of water and electrolytes and e) the actions and effects of certain diuretic drugs.

Starting and Stopping the Program

Begin by copying the *KIDNEY.EXE* program from the *bi374* folder my *Out Folder* to your hard drive. Start the *KIDNEY* program by double clicking on its desktop icon or selecting *Start | Run | Browse* and locating *KIDNEY.EXE* on your local hard drive. This will open a DOS window on your screen and prompt you for the date as shown below:

```
A SINGLE NEPHRON MODEL OF THE HUMAN KIDNEY - V87.0
  by Fred R. Sias, Jr. and Richard J. Roman
  Clemson University and the Medical College of Wisconsin

...

TYPE TODAY'S DATE (Example: 3/1/87) > 1/28/00
```

After entering the date, you will be prompted for the type of kidney to simulate as shown below:

```
Select the kidney you wish to simulate:
...
      1. Dog nephron
      2. Rat nephron
      3. Human nephron
...
Select <1, 2, or 3>:
```

At this point, enter 3 to simulate a human kidney. The following screen should then be displayed:

```
We are about to simulate a HUMAN nephron
  WITH glomerular-tubular feedback

      Normal Arterial Blood Pressure: 100

Select option (H for HELP):
```

The line *Select option (H for HELP):* is the main menu prompt for this program and is the starting point of each of the following exercises. All program input must be in

upper case so it is probably best to turn on Caps Lock at this point. Enter 99 at the main menu prompt to exit the program at any time. Lists of the abbreviations used in the program and these procedures are provided at the end of this document.

Determinates of GFR and RBF

Enter 17 at the Select option (H for HELP): main menu prompt to start the Lab GFR & RBF exercise. The following text should be displayed:

```

ALL PARAMETERS HAVE BEEN REINITIALIZED!
TUBULAR-GLOMERULAR FEEDBACK WILL NOT BE SIMULATED.

System automatically selects GFR, RBF, UF
Type name of any additional variable you wish to observe. Be sure to
use the proper mnemonics.

HUMAN Renal Study - 1/27/00 - This run WITHOUT feedback.

PARS:      CONTROL:
PART -    100.00000 mmHg          Mean arterial pressure

VARS:
GFR  -    126.22430 ml/min       Total renal glomerular filtration rate
RBF  -   1122.86900 ml/min       Total renal blood flow
UF   -     2.58476 ml/min       Total urine flow
PPERI -   24.61542 mmHg         Peritubular cap. hydraulic pressure
PGLOM -   53.21379 mmHg         Mean glomerular hydraulic pressure

DO YOU WISH TO CHANGE PARAMETERS? (Y or N)>

```

Note that tubular-glomerular feedback has automatically been disabled. You are about to adjust a series of renal variables and observe their impact on the GFR and RBF, but first complete the Expected Results table below with the symbols ↑ (increase), ↓ (decrease), ~ (remain unchanged) or ? (unsure or can't be predicted).

Determinates of GFR, RBF, etc. Expected Results –

	RAFF		REFF		KFGLOM		RVEN	
	↓	↑	↓	↑	↓	↑	↓	↑
GFR								
RBF								
UF								
PPERI								
PGLOM								

Enter Y in response to the DO YOU WISH TO CHANGE PARAMETERS? (Y or N)> prompt. You will see a PAR> prompt. Enter the name of the parameter you wish to change (RAFF in this case). Next, enter the new value for the parameter (in this case 0.2). To see the impact of your parameter change press enter at the PAR> prompt. You can change more than one variable at a time by entering their names at the PAR> prompt.

Determinates of GFR, RBF, etc. Observed Results –

	Control	RAFF		REFF		KFGLOM		RVEN	
		/2	x2	/2	x2	/2	x2	/10	x10
GFR (ml/min)									
RBF (ml/min)									
UF (ml/min)									
PPERI (mm Hg)									
PGLOM (mm Hg)									

Repeat this process to complete the observed results table. Remember to reset parameters back to their initial values before proceeding to study the next parameter. After completing the table, answer N to the DO YOU WISH TO CHANGE PARAMETERS? (Y or N) > prompt to return to the main menu.

Compare your expected and observed results. Compare and contrast the mechanisms and effects of renal artery stenosis (equivalent to increased RAFF) and glomerular sclerosis (decreased KFGLOM).

Tubular-Glomerular Feedback

In this excise you'll observe the effectiveness of the tubular-glomerular feedback in the control of RBF and renal function. You'll simulate renal function for a series of PART's with and without tubular-glomerular feedback. Before starting the simulation, Sketch the expected plots of RBF, GFR and UF versus PART with and without tubular-glomerular feedback.

Enter 18 at the Select option (H for HELP): main menu prompt to perform the first phase of the Autoregulation of GFR & RBF exercise. In this phase, tubular-glomerular feedback has been disabled. The values of the RBF, GFR, UF, TEXNA, TEXUR and TEXK will be displayed for a series of PART's. Record these values in the table below:

Effects of PART **without** Tubular-Glomerular Feedback, Results –

PART (mm Hg)	60.0	80.0	100	120	140	160	180	200
RBF(ml/min)								
GFR(ml/min)								
UF(ml/min)								
TEXNA(μmol/min)								
TEXUR(μmol/min)								
TEXK(μmol/min)								

Return to the main menu by pressing *Enter*. Enter 8 at the *Select* option (H for HELP) : prompt to activate tubular-glomerular feedback. Next, enter 18 at the main menu prompt to repeat the second phase of the Autoregulation of GFR & RBF exercise. In this phase, tubular-glomerular feedback will be enabled. The values of the RBF, GFR, UF, TEXNA, TEXUR and TEXK will again be displayed for a series of PART's. Record these values in the table below:

Effects of PART **with** Tubular-Glomerular Feedback, Results –

PART (mm Hg)	60.0	80.0	100	120	140	160	180	200
RBF(ml/min)								
GFR(ml/minn)								
UF(ml/min)								
TEXNA(μ mol/min)								
TEXUR(μ mol/min)								
TEXK(μ mol/min)								

Compare the results of these two phases of this exercise. Do the results match your expectations? Are GFR and RBF autoregulated over the same range of PART's? Plot some of your results (say RBF or GFR versus PART with and without feedback control).

Renal Hormonal Response

In this experiment you'll study how the concentrations of renin (HPRA), aldosterone (HALDO) and ADH (HADH) affect renal function. Begin by completing the table of expected results below:

Renal Hormonal Response, Expected Results –

	HPRA		HALDO		HADH	
	↓	↑	↓	↑	↓	↑
GFR						
RBF						
UF						
TEXK						
TEXNA						
TEXUR						
OURINE						

Next, simulate the renal response to changes in hormone concentrations using the program. Be sure tubular-glomerular feedback is activated before proceeding by entering 8 at the main menu prompt. Next, enter 19 at the main menu prompt to start the neural and hormonal control laboratory exercise. Change the values of the hormone concentrations to complete the observed results in the following table.

Renal Hormonal Response, Observed Results –

	Control	HPRA		HALDO		HADH	
		0	x3	0	x5	0	x2
GFR (ml/min)							
RBF (ml/min)							
UF (ml/min)							
TEXK (μ Eq/min)							
TEXNA (μ Eq/min)							
TEXUR (μ mol/min)							
OURINE (mOsm/l)							

Did your observations match your expectations? Do small changes in renin concentration primarily change the resistance of the afferent or efferent arteriole? How does changes in aldosterone concentration effect sodium and potassium excretion? Does ADH concentration effect the excretion of water or electrolytes or both? How do changes in ADH concentration effect urine osmolarity?

Return the main menu by answering *N* to the DO YOU WISH TO CHANGE PARAMETERS?
(Y or N)> prompt.

Renal Neural Response

The response of the kidneys to sympathetic tone is complex. Enter 19 at the main prompt to start a new simulation series. Answer *Y* to the DO YOU WISH TO CHANGE PARAMETERS? (Y or N)> prompt. Adjust the NRNA to values of 0, 1.5, 2.0, 2.5, 3.0 and 4.0 to complete the following table.

Renal Neural Response, Observed –

	NRNA (times normal)						
	0	1.0 (control)	1.5	2.0	2.5	3.0	4.0
GFR (ml/min)							
RBF (ml/min)							
UF (ml/min)							
TEXK (μ Eq/min)							
TEXNA (μ Eq/min)							
TEXUR (μ mol/min)							
OURINE (mOsm/l)							

Plot any three interesting variables (say GRF, TEXNA and OURINE) from this table versus NRNA.

Actions and Effects of Diuretics

Enter 20 at the main menu prompt to start the Lab Diuretics exercise.

Acetazolamide is an example carbonic anhydrase inhibitor. It significantly reduces bicarbonate reabsorption in the proximal tubule. In the program, the parameter THCO3P is the transport rate of bicarbonate in the proximal tubule. Reduce the value of THCO3P by a factor of 5 to simulate the action of Acetazolamide and record the results in the following table. What happens to the UF, OURINE, TEXNA and TEXK when the bicarbonate reabsorption is reduced? Why does the inhibition of bicarbonate reabsorption in the proximal tubule increase the excretion of sodium and water?

Furosemide is an example of a loop diuretic. It blocks chloride reabsorption, and thereby sodium reabsorption, in the loop of Henle. In the program, the parameter TNAH is the sodium transport rate in the ascending loop of Henle. Reduce the value of TNAH by a factor of 5 to simulate the action of Furosemide and record the results in the following table. How does effect of Furosemide on UF and TEXNA compare to that of acetazolamide?

Triamterene and spironolactone are examples of potassium sparing diuretics. They inhibit the reabsorption of sodium and the secretion of potassium in the aldosterone-sensitive portions of the distal tubule and collecting duct. In the program, the parameters TNACCD and TNAMCD are the sodium transport rates in the cortical and medullary collecting ducts, respectively. Reduce each of these values by a factor of 5 to simulate the

effect of these diuretics and record your results in the following table. Compare the urine flow and the ratios TEXNA/UF , TEXK/UF and TEXK/TEXNA for the control, Furosemide and the potassium sparing diuretic simulations. Is the diuretics' effect on urine flow and these ratios consistent with your expectations?

Actions and Effects of Diuretics –

	Control	Acetazolamide THCO ₃ P/5	Furosemide TNAH/5	K sparing diuretics TNACCD & TNAMCD/5
GFR (ml/min)				
RBF (ml/min)				
UF (ml/min)				
TEXK ($\mu\text{Eq}/\text{min}$)				
TEXNA ($\mu\text{Eq}/\text{min}$)				
TEXUR ($\mu\text{mol}/\text{min}$)				
OURINE (mOsm/l)				

Mnemonic Abbreviations used by the Program

Parameters (independent quantities, i.e. inputs), Default Values and Units

HADH	ADH concentration (3.00 pg/ml)
HALDO	Aldosterone concentration (8.00 ng/dl)
HPRA	Renin concentration (2.00 ngAI/ml/3hr)
KFGLOM	Glomerular filtration coefficient (3.80 (ml/min)/mm Hg)
NRNA	Renal nerve activity level (times normal)
PART	Mean arterial pressure (100 mm Hg)
RAFF	Afferent arteriole resistance (0.100 mm Hg/(ml/min))
REFF	Efferent arteriole resistance (0.0700 mm Hg/(ml/min))
RVEN	Venous resistance (0.053 mm Hg/(ml/min))
THCO3P	Bicarbonate transport in the proximal tubule (400 (pmol/min)/mm)
TNAH	Sodium transport in the loop of Henle (1000 (pmol/min)/mm)
TNACCD	Sodium transport in the cortical collecting duct (4.33 (pmol/min)/mm)
TNAMCD	Sodium transport in the medullary collecting duct (34.2 (pmol/min)/mm)

Variables (dependent quantities, i.e. outputs) and Units

GFR	Glomerular filtration rate (ml/min)
OURINE	Urine osmolarity (mOsm/l)
PGLOM	Glomerular hydraulic pressure (mm Hg)
PPERI	Peritubular capillary pressure (mm Hg)
RBF	Renal blood flow (ml/min)
TEXK	Total excreted potassium ($\mu\text{mol/min}$)
TEXNA	Total excreted sodium ($\mu\text{mol/min}$)
TEXUR	Total excreted urea ($\mu\text{mol/min}$)
UF	Total urine flow (ml/min)

Program Options (modes)

1. Output all variable at single arterial pressure.
2. Output variables at a sequence of pressures.
3. Perform a study.
4. Parameter sensitivity output.
5. Print parameters.
6. List system parameters.
7. Change parameters.
8. Add tubular-glomerular feedback.
9. Remove tubular-glomerular feedback.
10. Change output to printer (LPT).
11. Change output to screen (CRT).
12. Reset all parameters to normal values.
13. Print all names used in model.
14. Show parameter and variable names.
15. Case studies.
16. Plot graphical output.
17. GFR & RBF laboratory exercise.
18. Autoregulation laboratory exercise.
19. Neural hormonal control laboratory exercise.
20. Diuretics laboratory exercise.
99. Stop (exit from) the program.

Reference:

These experiments are based on those used at the Medical College of Wisconsin in the mid-1990's and on a computer simulation of renal function created by F. R. Sias and R. J. Roman in the late-1980's.