## Supplementary Material:

**Symbols and Abbreviations**

ACE – angiotensin converting enzyme

Aldo - aldosterone

ALH – ascending loop of Henle

ANGI - angiotensin I

ANGII – angiotensin II

AT1 – angiotensin receptor type 1

AT2 – angiotensin receptor type 2

B – degree of flow-dependent sodium reabsorption

cAT1 – AT1 receptor binding rate

cAT2 – AT2 receptor binding rate

CIS – renal interstitial sodium concentration

CNa – blood sodium concentration

Cprot – protein concentration

cvenous – venous compliance

CD – collecting duct

CNT – connecting tubule

CO – cardiac output

D – diameter

DCT – distal convoluted tubule

DLH – descending loop of Henle

ECF – extracellular fluid volume

Fi – water flow along tubule segment i

G – proportional controller gain

GFR – glomerular filtration rate

Kd, AngI – angiotensin I degradation nrate

Kd,AngII – angiotensin II degradation rate

Kd,renin – renin degradation rate

Kf – ultrafiltration coefficient

Ki – integral controller gain

L –segment length

LoH – loop of Henle

m – slope of feedback signal around the operating point

MNa,blood – amount of sodium in the blood

MNa,ECF – amount of sodium in the ECF

MAP – mean arterial pressure

MD – macula densa

MR – mineralocorticoid receptor

Nnephrons – number of nephrons

Na – Sodium

P – pressure

PBow – Bowman’s space pressure

Pgc – glomerular capillary pressure

Pmf – mean filling pressure

PI – proportional integral

P-N – pressure natriuresis

PRA – plasma renin activity

PRC – plasma renin concentration

PT – proximal tubule

QNa – rate of exchange of sodium/water between the ECF and blood, across the Na concentration gradient

Raa – afferent arteriole reisstance

Rea – efferent arteriole resistance

Rperitubular – peritubular vascular resistance

Rpreaff – preafferent resistance

Rvr – resistance to venous return

Ri,0 – nominal absolute rate of sodium reabsorption per unit length

Rpt – absolute rate of reabsorption per unit length

RBF – renal blood flow

RAAS – renin angiotensin aldosterone system

RIHP - renal interstitial hydrostatic pressure

RPP – renal perfusion pressure

RVR – renal vascular resistance

S – magnitude of feedback signal as X goes to infinity

SECrenin – renin secretion rate

SNGFR – single nephron glomerular filtration rate

SVR – systemic vascular resistance

TGF – tubuloglomerular feedback

TPR – total peripheral resistance

Vb – blood volume

Vecf – extracellular fluid volume

vp – vasopressin

X0 – setpoint

πgo-avg - average glomerular capillary oncotic pressure.

η – fractional rate of reabsorption

ΦNa,i – sodium flow along tubule segment i

μvasopressin – normalized vasopressin level

#### **Modeling Tubular Hydrostatic Pressure**

Hydrostatic pressure in the Bowman’s space is a key factor affecting GFR, and this pressure is influenced by both morphology and flow rates through the tubule. Changes in Na and water reabsorption along the nephron, which can occur either due to disease or treatments, can alter GFR by altering tubular pressures. Thus dynamically modeling tubular pressures can be critical to understanding GFR changes.

Adapting from Jensen et al(16), tubular flow rates described in the main text can be used to determine tubular pressure. The change in intratubular pressure dP\* over a length of tubule dx can be defined according to Poiseuille’s law as:

Eq. A1

Eq. 22 describes the relationship between transtubular pressure P and tubular diameter D, where Dc is the diameter at control pressure Pc, and β is the exponent of tubular distensibility (16).

Eq. A2

Substituting and assuming uniform interstitial pressure throughout the kidney, we obtain:

dx Eq A3

Integrating over a tubule segment length, we obtain inlet pressure as a function of the outlet pressure and the flow rate:

Eq A4

The pressure calculated at the inlet to the PT is used as PBow in Eq. 4 above.

Because the diameter of the CNT/CD changes as nephrons coalescence, calculating pressure along this segment is challenging. Under normal conditions, pressure drops 5-7mmHg across the CNT/CD (16). Thus, an effective control diameter was calculated to give this degree of pressure drop under baseline conditions.

#### **Modeling Glomerular Capillary Oncotic Pressure**

The glomerular capillary oncotic pressure is calculated using the Landis Pappenheimer equation, where Cprot is the concentration of protein at the point of interest.

Eq. A5

Plasma protein (Cprot-plasma) is assumed constant. Protein concentration at the distal end of the glomerulus (Cprot-glom-out) is determined as:

Eq. A6

Protein concentration is assumed to be varying linearly along the capillary length, and thus the oncotic pressure is calculated using the average of the plasma protein concentration and protein concentration at the distal end of the glomerulus.

The model does not account for filtration equilibrium, which occurs in some species.

#### **Control of Macula Densa Sodium Concentration by Tubuloglomerular Feedback**

Tubuloglomerular feedback (TGF) helps stabilize tubular flow by sensing Na concentration in the the macula densa, which sits between the LoH and DCT, and providing a feedback signal to inversely change afferent arteriole diameter. The TGF effect is defined as:

Eq. A7

The basal afferent arteriole resistance Raa is then multiplied by μTGF to obtain the ambient afferent arteriolar resistance. The setpoint CNa,MD,0 is the Na concentration out of the LoH and into the DCT in the baseline state at normal Na intake.

##### **Myogenic Autoregulation of Glomerular Pressure**

Glomerular hydrostatic pressure is normally tightly autoregulated, and changes very little in response to large changes in blood pressure. This autoregulation is in part through myogenic autoregulation of the preglomerular arterioles. While the pressure drop and thus myogenic response varies along the arteriole length, we make the simplifying assumption that the preafferent vasculature responds to control pressure at the distal end.

Eq. A8

Pressure at the distal end of the preafferent vasculature is given by:

Eq. A9

The basal preafferent arteriole resistance Rpreaff is then multiplied by μautoreg to obtain the ambient preafferent arteriolar resistance.

**Renin-Angiotensin-Aldosterone System Submodel**

Renin is secreted at a nominal rate SECren,0 modulated by macula densa sodium flow, as well as by a strong negative feedback from Angiotensin bound to the AT1 receptor.

Eq. A10

The macula densa releases renin in response to reduced sodium flow:

Eq. A11

We have found that the inhibitory effect of AT1-bound AngII on renin secretion can be well described by the following relationship:

Eq. A12

Plasma renin concentration (PRC) is then given by:

Eq. A13

Where ~~Krenin~~ Kd,renin is the renin degradation rate. PRA can be related to PRC by the conversion factor 0.06 (ng/ml/hr)/(pg/ml).

Angiotensin I is formed by PRA, assuming that its precursor angiotensinogen is available in excess and the plasma renin activity (PRA) is the rate-limiting step. AngI is also converted to AngII by the enzymes ACE and chymase, and is degraded at a rate of Kd,AngI.

Eq. A14

Angiotensin II is formed from the action of ACE and chymase on AngI, can be eliminated by binding to either the AT1 or AT2 receptors at the rate CAT1 and CAT2 respective, and is degraded at a rate of Kd,AngII.

II Eq. A15

The complex of Angiotensin II bound to the AT1 receptor is the physiologically active entity within the pathway, and is given by:

Eq. A16

AT1-bound AngII has multiple physiologic effects, including constriction of the efferent, as well and preglomerular, afferent, and systemic vasculature, sodium retention in the PT, and aldosterone secretion. Each effect is modeled as:

Eq. A17

where i represents the effect on efferent, afferent, preafferent, or systemic resistance, PT sodium reabsorption, or aldosterone secretion.

Aldosterone is the second physiologically active entity in the RAAS pathway, acting by binding to mineralocorticoid receptors (MR) in the CNT/CD and DCT to stimulate sodium reabsorption. MR-bound aldosterone is modeled as the nominal concentration Aldo,0 modulated by the effect of AT1-bound AngII, and the normalized availability of MR receptors (1 in the absence of an MR antagonist).

*\*MR* Eq. A18

The effects of MR-bound aldosterone on CNT/CD and DCT sodium reabsorption are modeled as:

Eq. A19

Where i is the CNT/CD or DCT.

**Calculation of Dependent Model Parameter Values Required for Steady State**

For some parameters, although a range may be established from the literature, it makes more sense to calculate the parameter based on values or setpoints for other parameters (while ensuring that the calculated value falls within the reported range). For instance, rather than specifying nominal systemic vascular resistance (SVR0), we can calculate what it must be to give the expected baseline cardiac output and MAP:

Eq. A20

Similarly, nominal renal vascular resistance (RVR0) can be calculated based on normal MAP and RBF values:

Eq. A21

Both peritubular vascular resistance (Rperitubular,0) and CNT/CD fractional reabsorption (ηCNT/CD,0) are difficult to measure precisely, and a wide range of values have been reported in the literature, primarily from non-human sources. For these parameters, also, we can instead calculate what their values must be to give specified steady-state values for more easily measureable parameters. Rperitubular,0 can be calculated based on the RVR0 calculated as given above, and reported values for afferent, efferent, and preglomerular resistances, which are known with greater certainty:

Eq. A22

Similarly, ηCNT/CD,0 can be calculated for a given equilibrium GFR, plasma Na concentration, and Na intake, as well as upstream fractional Na reabsorption rates, based on the fact that at equilibrium, Na excretion must equal Na intake (Φsodin). Na flow out of each segment can be calculated as:

Eq. A23

Eq. A24

Eq. A25

Na flow out of the CNT/CD must equal sodium intake:

= Eq. A26

Then, solving for ηcnt/cd,0 gives:

Eq. A27

There is substantial variability in experimental measurements of fractional Na reabsorption rates for each tubular segments. PT fractional reabsorption has been reported across the range of 40-78% (40-44). Under normal flow conditions, LoH fractional Na reabsorption has been reported from 85-93%(23, 45). For this analysis, fractional Na reabsorption rates in the PT, LoH, and DCT were set to 0.70, 0.88, and 0.5, respectively, and CNT/CD fractional reabsorption rate was calculated to be 0.827.