A Progressive Derivation of a Physiologically-Based ODE Model for Salt-Induced Hypertension

Modeling the Mechanisms of Salt Sensitivity

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Problem Statement

Formulate and analyze an ODE-based mathematical model to understand the role of salt intake in hypertension. For this, you should analyze scenarios of normal physiology as well as the case of hypertension.

Prepared for Mathematical Physiology & Systems Medicine

Abstract

This report develops a detailed, physiologically grounded ordinary differential equation (ODE) model to explain how salt intake influences blood pressure and contributes to hypertension, particularly in salt-sensitive individuals. Starting from first principles, the model is built step-by-step with biological reasoning, gradually increasing in complexity. Each component is supported by relevant literature, especially from Clemmer et al. (2017), to ensure physiological validity.

Key outcomes:

- A progressive ODE model capturing the relationship between salt intake and blood pressure
- Analysis of steady-state conditions in both normal physiology and salt-sensitive hypertension
- Quantification of the impact of salt sensitivity on blood pressure regulation

1 Introduction

1.1 Background on Hypertension and Salt Intake

- Hypertension significantly increases risk of cardiovascular diseases, kidney damage, and stroke
- Salt sensitivity refers to the degree of blood pressure response to changes in salt intake:
  - Salt-resistant individuals: minimal blood pressure changes with high salt intake
  - Salt-sensitive individuals: significant blood pressure increases with moderate salt intake
- Approximately 50% of hypertensive patients exhibit salt sensitivity

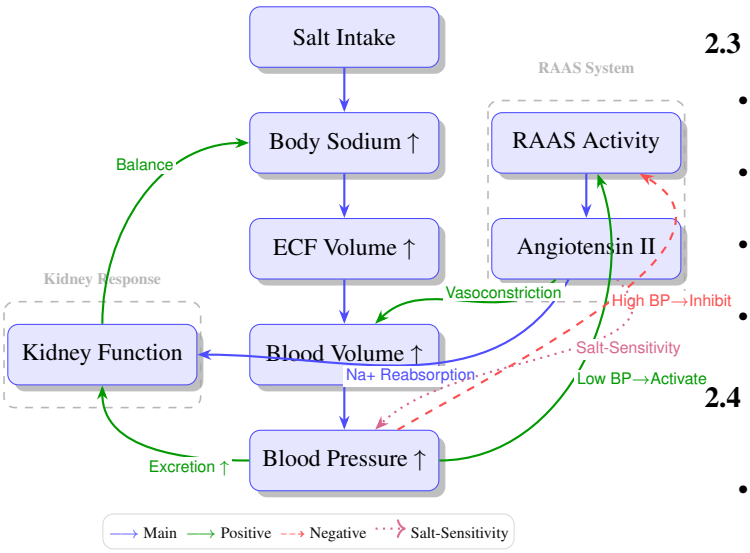

Figure 1: Salt, Blood Pressure, and Hypertension Regulation

1.2 Objectives of the Report

- Develop a mathematical model using ODEs to describe mechanisms linking salt intake to blood pressure regulation
- Provide intuitive biological reasoning for each model component
- Analyze both normal physiology and salt-sensitive hypertension
- Validate model components using experimental data from literature
- Extract clinical insights for personalized treatment approaches

2 Fundamental Physiological Concepts

2.1 Sodium Balance and Extracellular Fluid Volume

- Sodium (Na^+) is the primary cation in extracellular fluid (ECF)
- Body maintains sodium balance through:
  - Intake: dietary consumption
  - Output: primarily renal excretion
- Increased sodium intake leads to ECF volume expansion through osmotic water retention
- This volume expansion contributes to increased blood pressure

2.2 Blood Volume and Blood Pressure Relationship

- Blood pressure determined by:
  - Cardiac output (influenced by blood volume)
  - Total peripheral resistance (vascular tone)
- Changes in sodium balance affect blood volume, directly impacting blood pressure

2.3 Renal Function and Sodium Excretion

- Kidneys regulate sodium excretion through pressure-natriuresis
- Increased arterial pressure enhances sodium excretion
- This mechanism helps maintain sodium balance and blood pressure homeostasis
- In salt-sensitive individuals, this response is blunted

2.4 Hormonal Regulation: The Renin-Angiotensin-Aldosterone System (RAAS)

- RAAS plays pivotal role in blood pressure regulation by controlling:
  - Sodium retention
  - Vascular tone

- Key components:
  - Renin: released by kidneys when blood pressure drops
  - Angiotensin II: causes vasoconstriction, increasing resistance
  - Aldosterone: promotes sodium and water reabsorption
- In salt-sensitive individuals, RAAS may not adequately suppress during high salt intake

3 Progression of Model

3.1 Basic Volume Balance Model

Mathematical Formulation:

$$\frac{dV}{dt} = \gamma \left(I_{\text{Na}} - E_{\text{Na}} \right) \tag{1}$$

Key Parameters:
- V: Blood volume (L)
- I_{Na}: Sodium intake (mmol/day)
- E_{Na}: Sodium excretion (mmol/day)
- γ: Conversion factor (L/mmol)

Physiological Basis:
- $\gamma \approx 0.007$ L/mmol based on:
  - 1 mmol Na^+ retains approximately 6.5 mL ECF
  - About 20% of retained fluid is plasma
- Clemmer et al. (2017) observed direct relationship between salt intake and blood volume

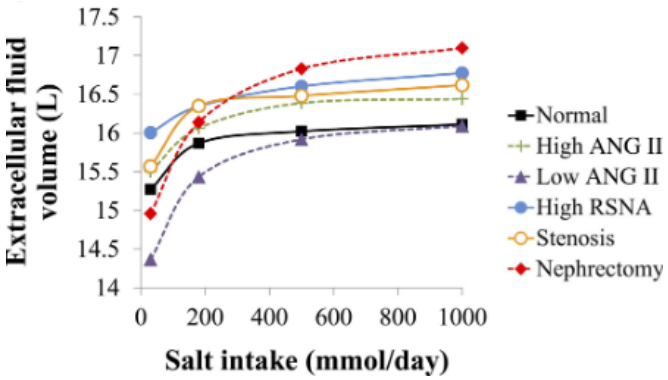

Figure 2: Experimental data showing pressure-natriuresis relationship (Clemmer et al., 2017)

3.2 Pressure-Dependent Sodium Excretion

Mathematical Formulation:

$$E_{\text{Na}}(P) = E_0 + \frac{E_{\text{max}} \cdot P^n}{P^n + P_{50}^n} \tag{2}$$

Key Parameters:
- E_0: Baseline excretion
- E_{max}: Maximum excretion capacity
- P_{50}: Pressure at half-maximal excretion
- n: Hill coefficient shaping response curve

Physiological Basis:
- Models pressure-natriuresis mechanism
- Higher blood pressure increases sodium filtration and excretion
- Sigmoidal response curve matches experimental observations

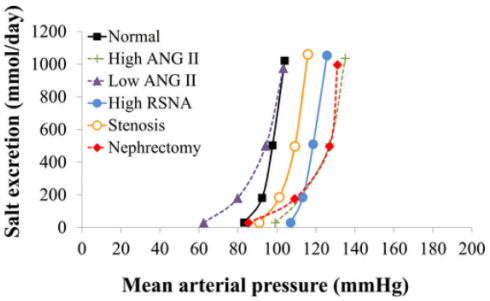

Fig. 10.

Renal function curve (pressure natriuresis curve) for each simulation is displayed as the MAP for a given salt excretion (or salt intake, since each data point is after 4 wk and represents a simulation that is in salt balance). Simulations with larger fluctuations in MAP during changes in salt intake are designated salt sensitive (dotted lines). These curves represent the steady-state MAP associated with each sodium intake and sodium excretion load for the various conditions.

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Figure 3: Experimental data showing pressure-natriuresis relationship (Clemmer et al., 2017)

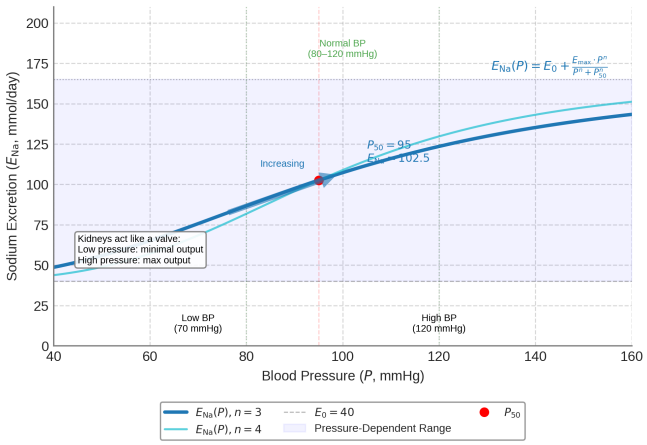

Figure 4: Pressure and Sodium Excretion

3.3 RAAS Modulation of Sodium Excretion

Mathematical Formulation:

$$E_{\text{Na}}(P, A) = E_0 + \frac{E_{\text{max}} \cdot P^n}{P^n + P_{50}^n} \cdot (1 - A) \tag{3}$$

Key Parameters:
- A: RAAS activity (0-1 scale)
- $(1 - A)$ term represents RAAS inhibition of excretion

Physiological Basis:

- High RAAS activity reduces sodium excretion via:
  - Angiotensin II effects on renal hemodynamics
  - Aldosterone-mediated sodium reabsorption

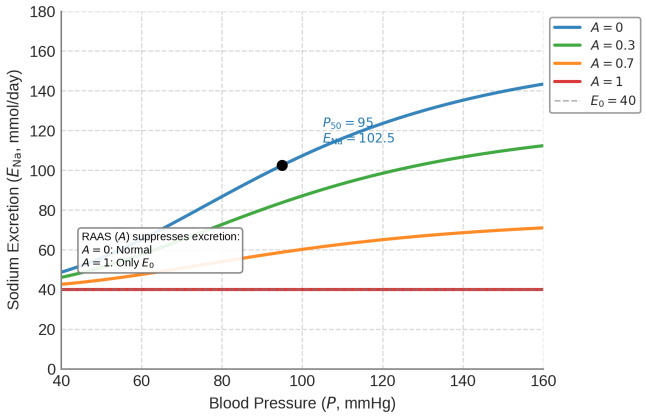

Figure 5: Final Pressure and Sodium Excretion

3.4 Modeling RAAS Dynamics

Mathematical Formulation:

$$\frac{dA}{dt} = \frac{1}{\tau_A}\left[\frac{A_{\max}}{1+\left(\frac{P}{P_0}\right)^m} - A\right] \tag{4}$$

Key Parameters:

- $A_{\max}$: Maximum RAAS activity
- P_0: Reference pressure
- m: Sensitivity coefficient
- τ_A: Time constant

Physiological Basis:

- RAAS activity decreases as pressure increases
- Negative feedback loop stabilizes blood pressure
- Time constant reflects delays in hormone synthesis and clearance

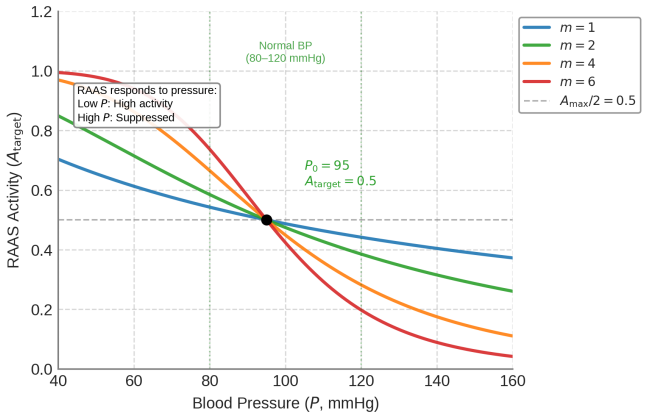

Figure 6: RAAS activity decreases as blood pressure increases

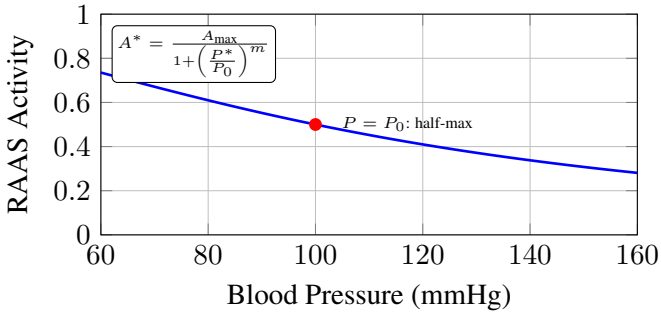

Figure 7: RAAS activity decreases as blood pressure increases

3.5 Incorporating Salt Sensitivity

Mathematical Formulation:

$$E_{\text{Na}}(P, A, \delta) = E_0 + \delta \cdot \frac{E_{\max} \cdot P^n}{P^n + P_{50}^n} \cdot (1 - A) \tag{5}$$

Key Parameters:

- δ: Salt sensitivity factor
  - $\delta = 1$: Normal renal function
  - $\delta < 1$: Salt-sensitive

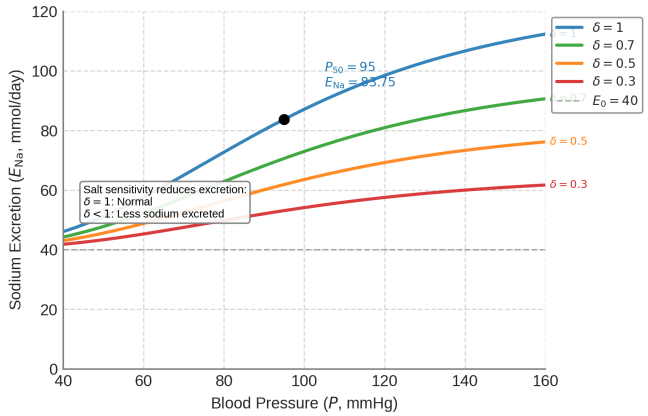

Figure 8: Sodium Excretion with Salt sensitivity

Physiological Basis:

- Salt sensitivity represents blunted pressure-natriuresis
- Lower values of δ indicate reduced sodium excretion capacity
- Physiological mechanisms include:
  - Reduced functioning nephrons
  - Enhanced tubular sodium reabsorption
  - Altered renal hemodynamics

3.6 Vascular Resistance Dynamics

Mathematical Formulation:

$$\frac{dR}{dt} = \frac{1}{\tau_R}\Big[R_0 + \alpha \cdot \frac{1}{\delta} \cdot A + \rho \cdot \frac{1}{1 + \left(\frac{P}{P_{\text{set}}}\right)^k} - R\Big] \tag{6}$$

Key Parameters:

- R: Total peripheral resistance
- R_0: Baseline resistance
- α: RAAS effect scaling factor
- ρ: Baroreflex contribution
- τ_R: Time constant for vascular adaptation

Physiological Basis:

- Vascular resistance affected by:
  - Baseline tone (R_0)
  - RAAS-mediated vasoconstriction (amplified in salt sensitivity by $\frac{1}{\delta}$)
  - Baroreflex-mediated vasodilation
- Salt sensitivity enhances vascular response to angiotensin II

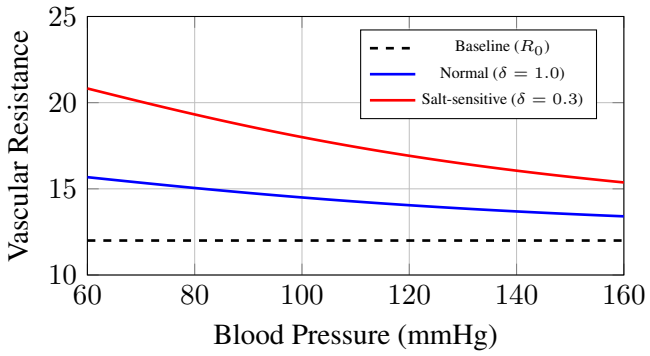

Figure 9: Total vascular resistance at steady state for different levels of salt sensitivity

3.7 Complete Blood Pressure Dynamics

Mathematical Formulation:

$$\frac{dP}{dt} = \frac{1}{\tau_P}\left(k_p \cdot V \cdot R - P\right) \tag{7}$$

Final ODE System:

$$\frac{dV}{dt} = \gamma\left[I_{\text{Na}} - \left(E_0 + \delta \cdot \frac{E_{\max} \cdot P^n}{P^n + P_{50}^n} \cdot (1 - A)\right)\right], \tag{8}$$

$$\frac{dA}{dt} = \frac{1}{\tau_A}\left[\frac{A_{\max}}{1 + \left(\frac{P}{P_0}\right)^m} - A\right], \tag{9}$$

$$\frac{dR}{dt} = \frac{1}{\tau_R}\left[R_0 + \alpha \cdot \frac{1}{\delta} \cdot A + \rho \cdot \frac{1}{1 + \left(\frac{P}{P_{\text{set}}}\right)^k} - R\right], \tag{10}$$

$$\frac{dP}{dt} = \frac{1}{\tau_P}\left(k_p \cdot V \cdot R - P\right). \tag{11}$$

Physiological Basis:

- Blood pressure determined by relationship between:
  - Blood volume (V)
  - Vascular resistance (R)
- Analogous to Ohm's law in electrical circuits
- Dynamic response with time constant τ_P

Table 1: Parameter calibration for the ODE model

Parameter	Description	Typical Value
γ	Volume per mmol Na^+	0.007 L/mmol
E_0	Baseline Na^+ excretion	30–50 mmol/day
$E_{\max}$	Maximum excretion capacity	100–150 mmol/day
P_{50}	Pressure for half-max excretion	90–100 mmHg
n	Excretion Hill coefficient	2–4
δ	Salt sensitivity factor	0.3–1.0
R_0	Baseline resistance	1–2 mmHg·min/L
α	RAAS effect on resistance	0.2–0.5 mmHg·min/L
ρ	Baroreflex contribution	0.2–0.4 mmHg·min/L
τ_A	RAAS time constant	10–60 min
τ_R	Resistance time constant	1–5 min
τ_P	Pressure time constant	1–10 min

4 Steady State Analysis

4.1 Foundations of Steady State Analysis

At steady state, all variables remain constant over time, meaning all derivatives equal zero. This represents the long-term stabilized condition of the system.

Key Steady State Conditions:

- Sodium intake equals excretion
- Blood volume is stable
- RAAS activity reaches equilibrium
- Vascular resistance stabilizes
- Blood pressure maintains a constant level

4.2 Solving for Steady State Values

4.2.1 Steady State RAAS Activity

Setting $\frac{dA}{dt} = 0$ yields:

$$A^* = \frac{A_{\max}}{1 + \left(\frac{P^*}{P_0}\right)^m} \tag{12}$$

Physiological meaning:

- RAAS activity decreases as pressure increases
- At normal pressure ($P^* = P_0$), RAAS is at half-maximal activity
- Hypertensive individuals typically have suppressed RAAS activity

4.2.2 Steady State Vascular Resistance

Setting $\frac{dR}{dt} = 0$ yields:

$$R^* = R_0 + \alpha \cdot \frac{1}{\delta} \cdot \frac{A_{\max}}{1 + \left(\frac{P^*}{P_0}\right)^m} + \rho \cdot \frac{1}{1 + \left(\frac{P^*}{P_{\text{set}}}\right)^k} \tag{13}$$

Physiological meaning:

- Vascular resistance depends on:
  - Baseline tone (R_0)
  - RAAS-mediated constriction (amplified by $\frac{1}{\delta}$ in salt sensitivity)
  - Baroreflex-mediated dilation
- Salt-sensitive individuals ($\delta < 1$) have greater RAAS-dependent vasoconstriction

4.2.3 Steady State Blood Pressure and Volume

Setting $\frac{dP}{dt} = 0$ and $\frac{dV}{dt} = 0$ yields:

$$P^* = k_p \cdot V^* \cdot R^* \tag{14}$$

$$I_{\text{Na}} = E_0 + \delta \cdot \frac{E_{\max} \cdot (P^*)^n}{(P^*)^n + P_{50}^n} \cdot (1 - A^*) \tag{15}$$

Physiological meaning:

- Blood pressure must reach a level where sodium excretion equals intake
- Salt-sensitive individuals require higher pressure to achieve sodium balance
- The steady state volume can be calculated as:

$$V^* = \frac{P^*}{k_p \cdot R^*} \tag{16}$$

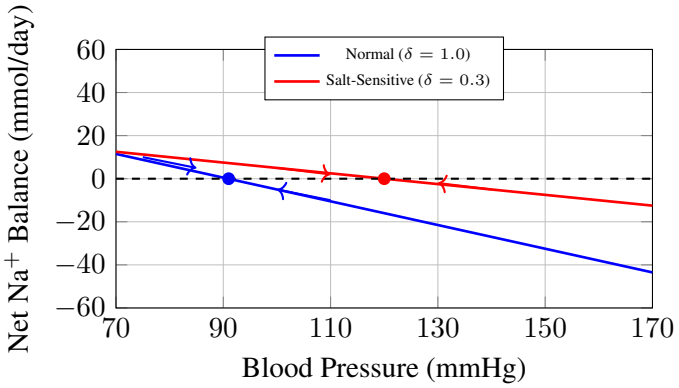

Figure 10: Net sodium balance as a function of blood pressure

4.3 Effect of Salt Intake on Blood Pressure

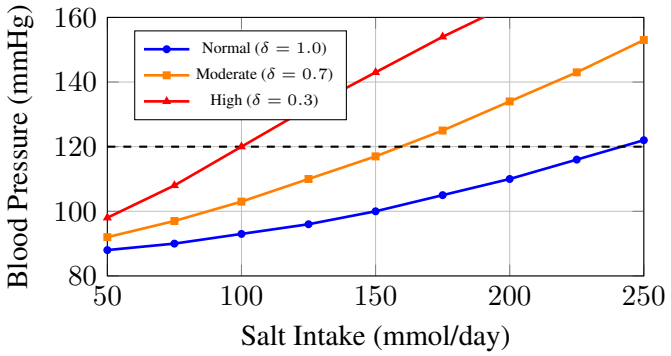

Figure 11: Relationship between salt intake and steady state blood pressure for different levels of salt sensitivity

4.4 Dynamic Response to Changes in Salt Intake

The model predicts different time courses in response to increased salt intake.

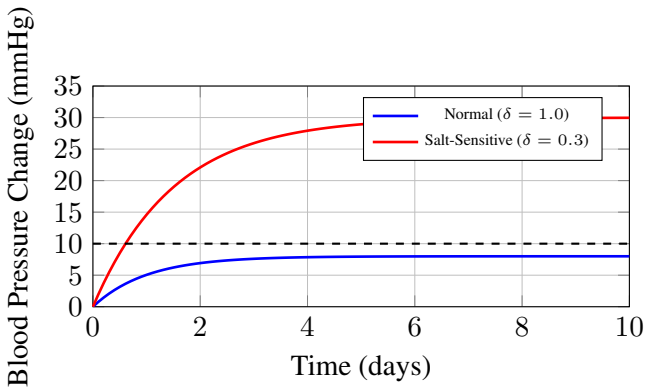

Figure 12: Blood pressure response to increased salt intake

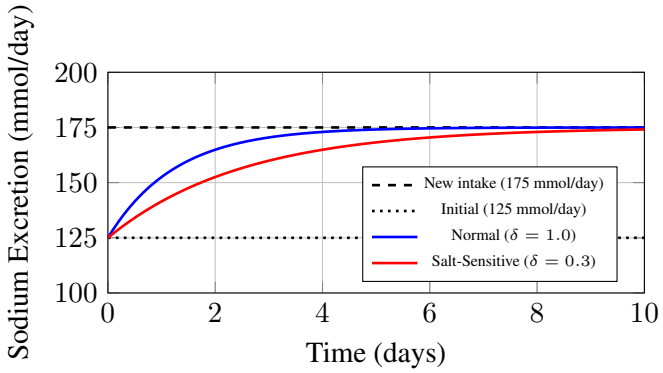

Figure 13: Sodium excretion response to increased salt intake

5 Clinical Implications

5.1 Identifying Salt Sensitivity

- The model suggests methods to estimate an individual's δ value:
  - Measuring blood pressure responses to controlled salt intake changes
  - Analyzing response to diuretics
  - Evaluating sodium excretion at different pressure levels

5.2 Personalized Treatment Approaches

- **Salt-sensitive patients benefit most from:**
  - Strict sodium restriction
  - Diuretics (enhancing sodium excretion)
  - ACE inhibitors/ARBs (blocking enhanced angiotensin II effects)
- **Less salt-sensitive patients may respond better to:**
  - Calcium channel blockers
  - Beta-blockers
  - Moderate salt restriction

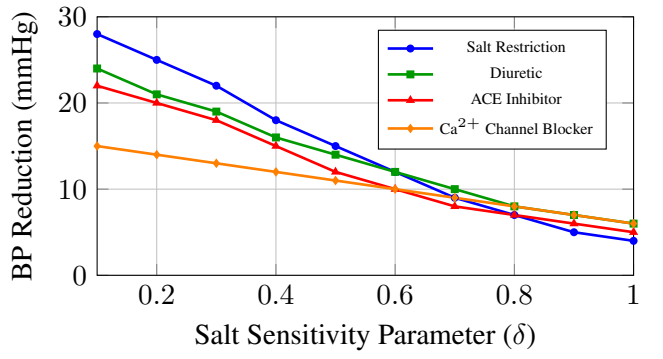

Figure 14: Treatment effectiveness based on salt sensitivity

5.3 Understanding Treatment Resistance

- Individuals with very low δ values may require:
  - Multiple medication classes
  - More aggressive salt restriction
  - Higher medication doses
- The model explains why some patients don't respond well to single-drug therapy
- Combined approaches targeting both excretion and vascular effects may be necessary

6 Key Insights and Conclusion

6.1 Physiological Insights

- **Pressure-natriuresis is central to long-term blood pressure control:**
  - Blood pressure must reach a level where sodium excretion equals intake
  - In salt-sensitive individuals, this requires significantly higher pressure
- **Salt sensitivity has dual mechanisms:**
  - Reduced renal sodium excretion (parameter δ)
  - Enhanced vascular sensitivity to angiotensin II (parameter $\frac{1}{\delta}$)
- **RAAS suppression doesn't prevent salt-sensitive hypertension:**
  - Despite lower RAAS activity at high pressure
  - Enhanced vascular sensitivity to angiotensin II compensates
  - Explains low-renin hypertension in some patients

6.2 Mathematical Contributions

- Progressive development of physiologically grounded ODE model
- Parameter δ captures salt sensitivity in both kidney and vascular components
- Steady state analysis provides quantitative relationships between:
  - Salt intake and blood pressure
  - Salt sensitivity and treatment response
  - RAAS activity and vascular resistance
- Time course predictions align with clinical observations

6.3 Clinical Value

- Framework for personalizing hypertension treatment based on salt sensitivity
- Explanation for variability in treatment response

- Rationale for combination therapy in resistant hypertension
- Identifies salt-sensitive patients as a high-priority group for salt restriction

6.4 Future Directions

- Clinical validation of model predictions
- Expansion to include:
  - Genetic factors in salt sensitivity
  - Immune system contributions
  - Long-term adaptation mechanisms
- Development of clinical tools to estimate individual salt sensitivity
- Model-guided optimization of multi-drug therapy

7 References

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