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ORIGINAL RESEARCH

How Much Sodium Should We Eat?

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ABSTRACT

Introduction: Sodium, an important dietary requirement, is essential to many physiologic processes. High sodium intake affects serious health issues such as hypertension and cardiovascular disease, the largest cause of death globally. Consequently, many health organizations have recommended substantial reductions in sodium intake, to as little as 1,500 mg/d. Yet limited understanding exists for the entire range of the effect of sodium between high intake and the recommendations.

Methods: We built a simulation using equations from the Uttamsingh model of the renal system to simulate the long-term mean arterial pressure (MAP) across sodium intake ranges. We used another existing physiology simulation platform, HumMod-3.0.4, for comparison. We compared the simulation results with empirical studies done on the global population.

Results: We find a linear increase in MAP for consumption above 4,000 mg/d, but nearly constant MAP between 1,200 and 4,000 mg/d. Below 1,200 mg/d, the system cannot maintain homeostasis.

Conclusion: Supporting the U-shape theory of sodium intake, which posits that too-high and too-low sodium intake rates increase cardiovascular disease risks, our results suggest that the homeostatic regulation by antidiuretic hormone and aldosterone transitions from sodium retention to sodium excretion at around 4,000 mg/d (a value that varies across individuals and conditions), indicating sodium saturation and evolutionary optimality. Our findings are consistent with recent empirical studies on large populations globally. We suggest that the current low-level recommendations are not supported by this physiologic model analysis and would require more compelling evidence.

Keywords: **physiology simulation; sodium intake; sodium reduction**

Introduction

Sodium is essential to many physiologic processes and is, thus, an important dietary requirement.[1] In particular, adequate sodium is fundamental to survival because intravascular volume is dependent on sodium and water.[2] However, sodium levels can be a factor in serious health issues such as hypertension and cardiovascular disease (CVD). A large body of evidence associates high sodium intake (>5,000 mg/d) with CVD, which is the major cause of death globally,[1] prompting the U.S. Departments of Agriculture and Health and Human Services to recommend reducing dietary sodium to 2,300 mg/d to limit damaging outcomes of CVD.[3–7] The American Heart Association recommends intake below 1,500 mg/d,[7] whereas the World Health Organization (WHO) advises <2,000 mg/d.[8]

Although much attention has focused on the harm of high sodium intake, limited understanding exists for the range between high intake and the recommended level. Similarly, the potential benefits of sodium reduction to the low range have little empirical support,[2] whereas the potential dangers are also not well understood.[9] An ongoing debate on the nature of the relationship between sodium intake and human health is at issue. A report from the Institute of Medicine found no evidence that reduction in sodium to below 2,300 mg/d reduces the risk of heart attack, stroke, or death.[10] A meta-analysis of randomized controlled trials[11] found no effect on all-cause mortality among obese hypertensive or prehypertensive people after sodium reduction to 2,300 mg/d, whereas healthy populations showed only 1 mm Hg difference in blood pressure. Large-scale reviews of experimental results have led some to conclude that a paucity of high-quality evidence cannot guide public health policy, and in fact, current guidelines bear no physiologic relevance.[2,9] Others have noted that there is no policy consensus on optimal sodium intake or on the harm or benefit of reducing sodium below the United States' average.[12]

On the other hand, there is evidence that recommended reductions may not be achievable. Approximately 90% of the world's population has an average sodium intake of 2,600–5,000 mg/d, a figure consistent throughout 50 years of research across 45 countries in multiple ethnic groups.[2,13] People in the U.S. consume 3,400–3,600 mg/d on average.[2,10,12] On a global scale, 6–7 billion people would have to alter their diets to accommodate these recommendations.[11] Furthermore, according to Heaney,[12] "given available foods, these levels have been found to be difficult if not impossible to achieve in a diet otherwise adequate in total nutri-

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ents." Other researchers agree on the difficulty of maintaining such sodium restrictions.[9,14–16] Furthermore, many countries with high sodium intake (eg, Japan and Finland) have high life expectancy, whereas stroke rates in the United States have been declining for 25 years despite a constant level of sodium consumption.[1]

Two models seem to drive the overall debate, which has extended for >20 years.[17] The first assumes that reduction in sodium intake produces a positive effect with no other consequences. The second posits that sodium consumption rates that are too low as well as too high increase the risk of all-cause mortality and CVD. For example, based on results of randomized studies performed in high- and low-sodium environments, risks increased significantly for those assigned a low intake of 1,800 mg/d, and risks increased for those assigned a high intake of 5,300 mg/d.[18] Sodium intake in the normal range was consistent with optimal health outcomes.[2] This is the so-called U-shape model.[2,12,18,19]

This article aims to add to this discussion by using existing models of physiology to simulate long-term mean arterial pressure (MAP) across a range of dietary sodium levels. We simulate the long-term MAP using 2 physiologic models, the Uttamsingh model[20] and HumMod-3.0.4 model (referred to as "HumMod" in the following).[21] We find, however, that HumMod produces some results inconsistent with empirical results. So our report focuses on the results yielded by the Uttamsingh model. We find, consistent with the harmful effect of high sodium consumption, that there is a linear increase in MAP for consumption levels above 4,000 mg/d. Between 1,200 and 4,000 mg/d, MAP remains approximately constant. Below 1,200 mg/d, the system is unable to maintain homeostasis, suggesting that physiologic anomalies may occur in this range. This conclusion is subject to the limitations of the model because of the methods by which it was constructed. Our results, however, point to the need for further experiments to map the physiologic space and its connections to medical outcomes. By considering the mechanisms underlying the different regimes of behavior, we find that the homeostatic regulation by antidiuretic hormone (ADH) and aldosterone (ALD) leads to sodium retention below 4,000 mg/d sodium intake and sodium excretion above 4,000 mg/d, suggesting the transition point of 4,000 mg/d as an indicator of sodium saturation and evolutionary optimality.

Methods

We simulated the MAP based on a range of sodium intakes with 2 different simulation platforms: one with the Uttamsingh model[20] and the other with HumMod software (http://hummod.org/). The Uttamsingh model of renal circulation is developed based on the fundamental Guyton model[22] and has been validated against several sets of experimental data.[23] HumMod is an integrative mathematical model that consists of 5,000 variables describing whole-body physiology.[21] Because HumMod is well documented in its supplementary files, in this section, we focus on the way we implemented the Uttamsingh model.

The Uttamsingh model has 4 components relevant to sodium circulation: the cardiovascular system, kidney system, hormonal subsystems, and fluid electrolyte balance. Fig 1 illustrates their interactions.

The Uttamsingh model considers 3 input variables: the intake of water, of sodium, and of potassium. The model has 64 dynamic variables that are computed at 1-minute intervals, 7 of which are required as inputs in addition to intakes for each iteration:
W = total body water,
TENA = total extracellular sodium,
TEK = total extracellular potassium,
ADH = concentration of ADH,
ALD = concentration of ALD,
A = concentration of angiotensin II, and
R = concentration of renin.

We simulate this model for a reference 70-kg male, determining the fixed parameters of the model accordingly. The initial total body water, W, is calculated using the Watson formula.[24] The initial values for the other 6 key variables are set according to the reference value for a healthy human. Fifty-seven additional intermediate variables are calculated based on the key variables (along with other parameters and reference values of the model), together representing the set of physiologic measures at a given time. The changes per minute of the 7 variables are calculated according to the dynamic equations of Uttamsingh.[20] The change per minute of 4 variables, ΔADH, ΔALD, ΔA, and ΔR, depends on internal measures only. The other 3, ΔW, ΔTENA, and ΔTEK, depend on external inputs of water, sodium, and potassium, respectively. For example,

$$\Delta TENA = SODMIN - UNA \quad (1)$$

SODMIN represents sodium intake at each minute, and UNA represents sodium excretion at each minute. The 7 key variables of the next minute are defined as:

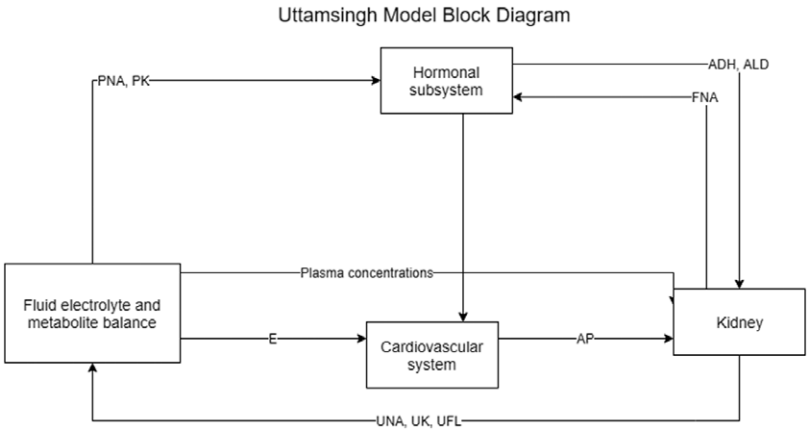

Fig 1. Uttamsingh model block diagram. Boxes represent the 4 components: the cardiovascular system, kidney system, hormonal subsystems, and fluid electrolyte balance. Arrows indicate interactions between the components via the physiologic variables shown in their labels. E indicates extracellular fluid volume; FNA, filtered load of sodium; PK, potassium concentration in plasma; UK, potassium excretion rate in urine.

$$X_t = X_{t-1} + \Delta X_{t-1} \quad (2)$$

X is in the set of W, TENA, TEK, ADH, ALD, A, and R.
For the other 57 intermediate variables y_i, $i = 1, 2, ..., 57$,

$$y_{i,t} = F_i\left(W_t, TENA_t, TEK_t\ ADH_t, ALD_t, A_t, R_t\right) \quad (3)$$

where F_i is specified explicitly in the Uttamsingh model.[20] The system is iterated until a designated simulation end time. For convenience, the simulation was programmed in Python and the data are stored as Pandas dataframes.

We adhered to the WHO recommendation for mean water intake of 2.5 L/d and potassium intake of 90 mmol/d.[25,26] We also performed a sensitivity analysis to evaluate the change in key results to the variation of water and potassium intake away from the recommended levels.

We simulate 5 different input cases: constant, oscillating wave, square wave, uniform, and Gaussian random inputs. For the results reported in this article, we use constant inputs. Oscillating waves, square waves, and uniform random inputs yield similar results.

Results

Comparison of the Uttamsingh model and HumMod

The results from the 2 simulations are shown in Fig 2. For the Uttamsingh model, MAP increases in range C (>4,000 mg/d). In range B (between 1,200 and 4,000 mg/d), MAP is nearly independent of sodium intake except for a dip near 4,000 mg/d. Below 1,200 mg/d, MAP is high and unstable, increasing without bound. This anomalous behavior is discussed in Section 3.3. For HumMod, in range A, MAP decreases to a minimum at 700 mg/d, then increases. MAP keeps increasing in ranges B and C as sodium intake increases, but more rapidly in the middle intake range than in the high range.

The results are compared with an empirical study by Rodrigues et al.[27] The orange dashed line in Fig 2 shows the MAP calculated by the adjusted diastolic and systolic blood pressure (DBP, SBP) found in their study using the usual approximation:

$$MAP = DBP + \frac{SBP - DBP}{3}$$

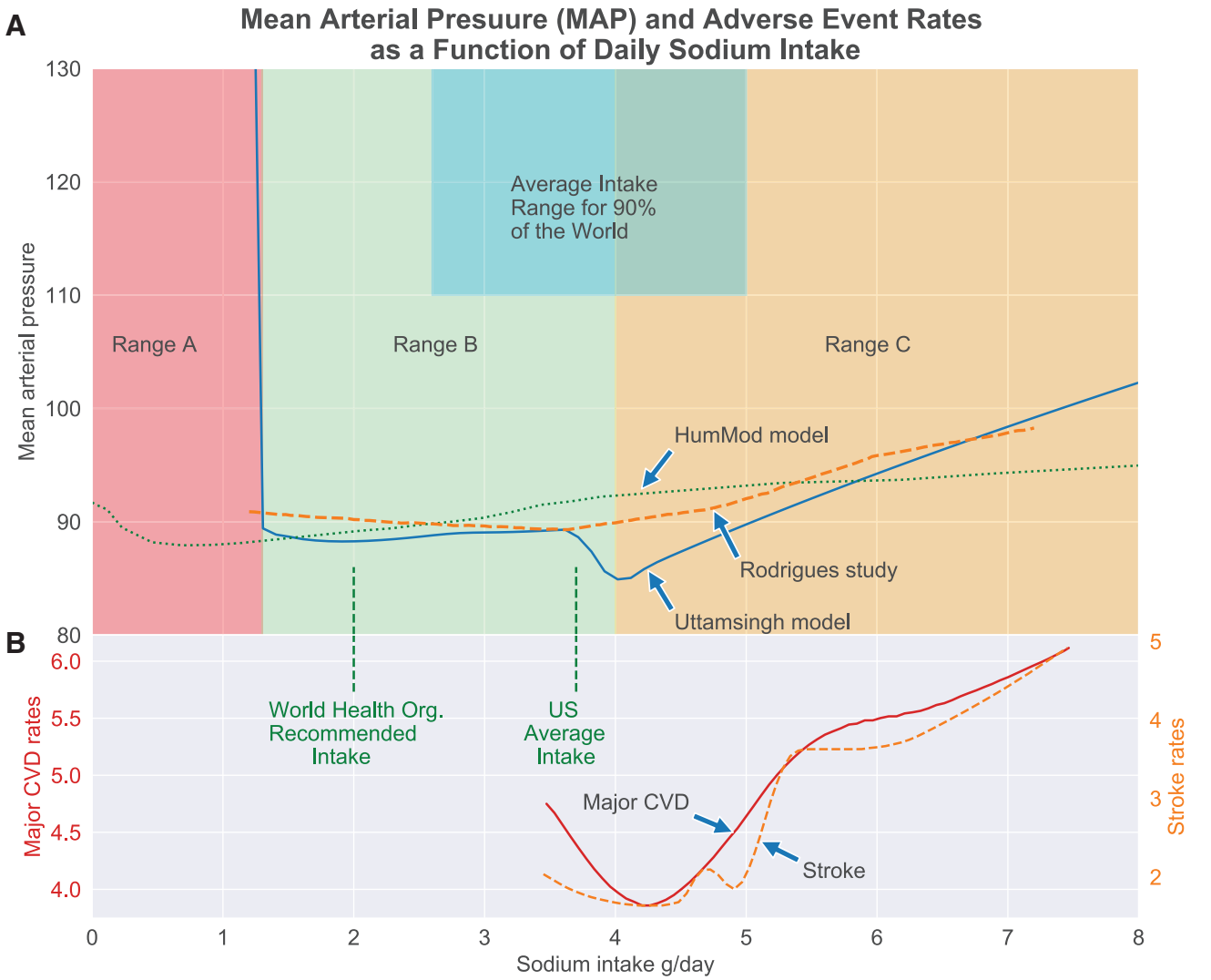

Fig 2. MAP and adverse event rates as a function of daily sodium intake. A, The simulated MAP of a 70-kg reference male after 7 days is shown. HumMod simulation (green dotted line) and the Uttamsingh simulation after 100-mg range smoothing (blue curve) are compared with empirically observed, population-averaged MAP (orange dashed line).[27] The Uttamsingh model in range A (sodium intake <1,200 mg/d) shows unstable behavior (Section 3.3). MAP simulated with the Uttamsingh model is nearly constant in range B (1,200–4,000 mg/d), with a dip around 4,000 mg/d and almost linearly increasing in range C (>4,000 mg/d). MAP simulated with HumMod is decreasing in the range of 0–700 mg/d, comparatively rapidly increasing in the range of 700–3,500 mg/d, and then slowly increasing beyond the daily consumption of 3,500 mg/d. B, The result from a recent study by Mente et al[19] is shown. The 2 curves represent the cardiovascular event rates (events per 1,000 person-years) for major CVD (red curve) and stroke (orange curve), respectively, based on dietary sodium intake.

The results are also compared with the Prospective Urban Rural Epidemiology (PURE) study (the lower pane in Fig 2), which shows the cardiovascular event rates based on sodium intakes.[19] The data of the PURE study are averaged across 369 communities ranging from 3,220 to 7,520 mg/d. We note that parts of the PURE study use memory-based questionnaires to assess nutrition intakes,[28] and this memory-based method is widely criticized.[29,30] However, the results we cite use urinary sodium excretion rather than dietary recall to estimate sodium intake.[19] The urinary method has been validated as a surrogate for sodium intake,[31] despite the potential importance of sodium excretion in sweat.

Effect of sodium intake on MAP

The average sodium intake for approximately 90% of the world's population is in the range of 2,600–5,000 mg/d[2,13] (blue-shaded region in Fig 2), and in the United States, the average is estimated to be in the range of 3,400–3,600 mg/d.[2,10,12] In contrast, WHO advises an intake of <2,000 mg/d.[8] The Uttamsingh model result does not support the necessity of a further sodium reduction from the status quo to as low as the recommended level.

To show the dynamics that give rise to the Uttamsingh result of Fig 2, we show the minute-by-minute MAP for ranges B and C in Fig 3. In range B (the green–purple curves), the MAP decreases and then increases to the stabilized value, which is nearly independent of sodium intake within the range of 1,200–4,000 mg/d. The decrease is an artifact due to the model adjusting its initial values to those that are physiologically relevant. Therefore, this is not to be expected in actual behavior. In range C (>4,000 mg/d, the orange–red dashed curves), the MAP grows asymptotically to its stabilized value.

We investigated the reasons for this separation of regimes and identified 2 system properties that are relevant: the nonlinear relationships of water and sodium reabsorption based on ADH and ALD.

The arterial pressure (AP) is determined mainly by total body water (W):

$$AP = CO \times TPR = \frac{MSP - RAP}{0.07 \times TPR} \times TPR \approx 6.13W - 155 \quad (4)$$

The change per minute of total body water (ΔW) is the difference between water intake (FLUMIN) and urine flow rate (UFL).

$$\Delta W_i = FLUMIN - UFL_i \quad (5)$$

The urine flow rate is as follows:

$$UFL = \frac{EFLH \times (EFLH + 35)}{100} \times (1 - EBDT) \quad (6)$$

EFLH is the flow rate of water into the loop of Henle, and EBDT is the fraction of water load reabsorbed from the distal nephron tubules. EFLH can be shown to be given by:

$$EFLH = \frac{5000 \times SFDT}{PNA} \quad (7)$$

PNA stands for the extracellular sodium concentration, and SFDT stands for the flow rate of sodium into the distal tubule. Because PNA is tightly regulated, EFLH is approximately proportional to SFDT, which is linearly associated with sodium intake. Thus, EFLH is positively correlated with sodium intake.

The regulation of total body water requires that ΔW be approximately 0 in steady state, which is the long-term condition in ranges B and C. Thus from equation (5),

$$FLUMIN \approx UFL = \frac{EFLH \times (EFLH + 35)}{100} \times (1 - EBDT) \quad (8)$$

EFLH rises as sodium intake increases. To match FLUMIN, the (1− EBDT) term has to decrease. EBDT as a function of ADH is plotted in Fig 4.

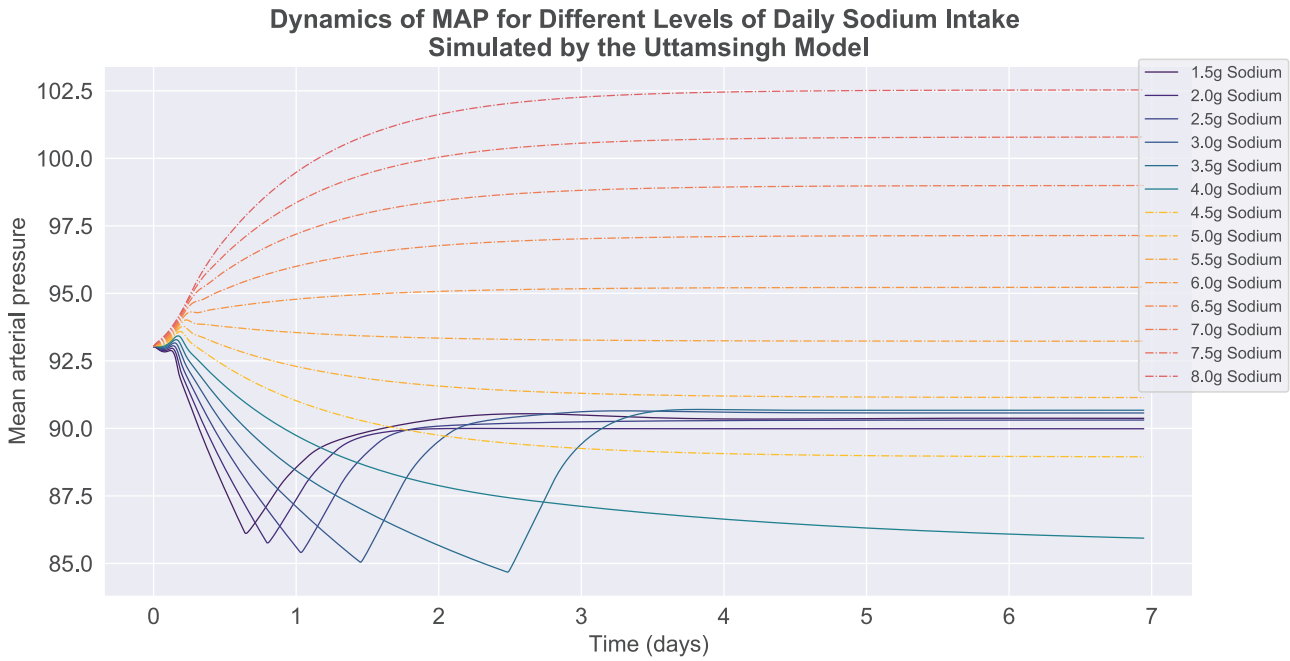

Fig 3. Dynamics of MAP for different levels of daily sodium intake simulated by the Uttamsingh model. Each color represents the dynamics for a specific daily sodium level, ranging from 1,500 to 8,000 mg/d. The green curves represent the APs of range B (1,200–4,000 mg/d). The orange dashed ones represent range C (4,000–8,000 mg/d), which increase linearly as sodium intake grows.

The slope of EBDT with regard to ADH dramatically decreases around ADH = 3.95 munit/L, which also is the boundary between the ADH for ranges B and C. For range B, with an increase in sodium intake, EBDT increases to match the urine output with water intake, thus stabilizing the total body water. For range C, with the increase in sodium intake, ADH accumulates but EBDT reaches its upper bound, thus ceasing to regulate total body water effectively. This is reflected in the increase in the system's regulation time to reach a stabilized state as sodium intake increases in range C.

The second regulatory factor is the concentration of ALD. The sodium flow rate in urine (UNA) is the difference between SFDT and the sodium reabsorption ratio (SDTR), which is mediated by ALD. In range B, ALD concentration is generally above 85 ng/L (on the right in Fig 4). Within this range, SDTR as a function of ALD has a smaller slope compared with range C, which has an ALD concentration below 85 ng/L. The 2 ranges once again reside on 2 parts of a nonlinear function.

Confirming the hypothesis that the separation of 2 regimes results from the nonlinearity of ADH and ALD, we replace the ADH versus EBDT and ALD versus SDTR functions with a wider linear range counterpart (the dashed lines in Fig 4). The resulting dynamics are plotted in Fig 5. We see that there is no sodium-independent regime. The resulting MAP is generally linearly associated with the daily sodium intake.

ADH and ALD together regulate the water/sodium balance of the body. Based on different sodium intakes, the reabsorption ratio of water and sodium in the distal tubule is plotted in Fig 6. In range B, a lower fraction of water is reabsorbed although the system retains a high percentage of sodium. In range C, sodium is eliminated at a progressively higher ratio as sodium intake increases, indicating sodium saturation. As a result, based on the way EBDT and SDTR are defined by ADH and ALD, respectively, ranges B and C are 2 distinct physiologic regimes, in which the former retains sodium and the latter excretes sodium.

Anomalous behavior for low sodium intake in the Uttamsingh model

As noted earlier for low sodium intake (<1,200 mg/d), the MAP from the simulation grows without bound. Upon examining the dynamics, we find the sodium concentration in plasma (PNA) drops rapidly, to the point of hyponatremia (a condition defined as

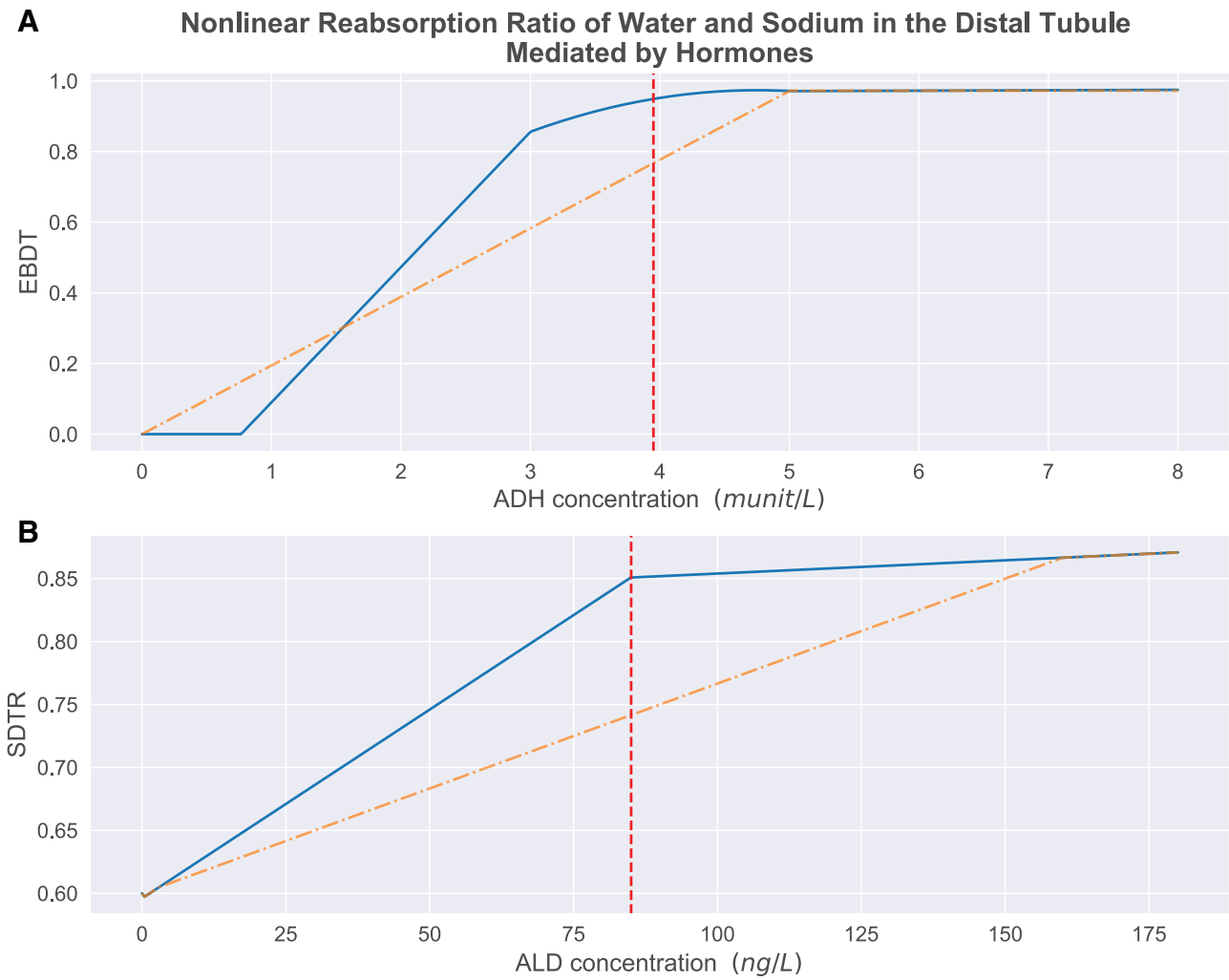

Fig 4. Nonlinear reabsorption ratio of water and sodium in the distal tubule mediated by hormones. A, The fraction of water load reabsorbed in the distal nephron segments (EBDT) as a function of ADH concentration in blood plasma is shown. The red line (ADH = 3.95 munit/L) separates ranges B and C. In range B (ADH lies below 3.95), EBDT increases as a function of ADH concentration, whereas in range C (ADH lies above 3.95), it is almost constant. B, The reabsorption ratio of sodium in the distal convoluted tubule (SDTR) as a function of ALD concentration in blood plasma is shown. The red line (85 ng/L) separates ranges B and C, with range B to the right and C to the left. Although the SDTR of both range B (ALD lies above 85 ng/L) and range C (ALD lies below 85 ng/L) increases as ALD increases, it increases in range C at a much greater rate than in range B. A and B, The orange dashed line shows a linear counterpart used to test the hypothesis that the nonlinearity of these 2 functions gives rise to the different regimes.

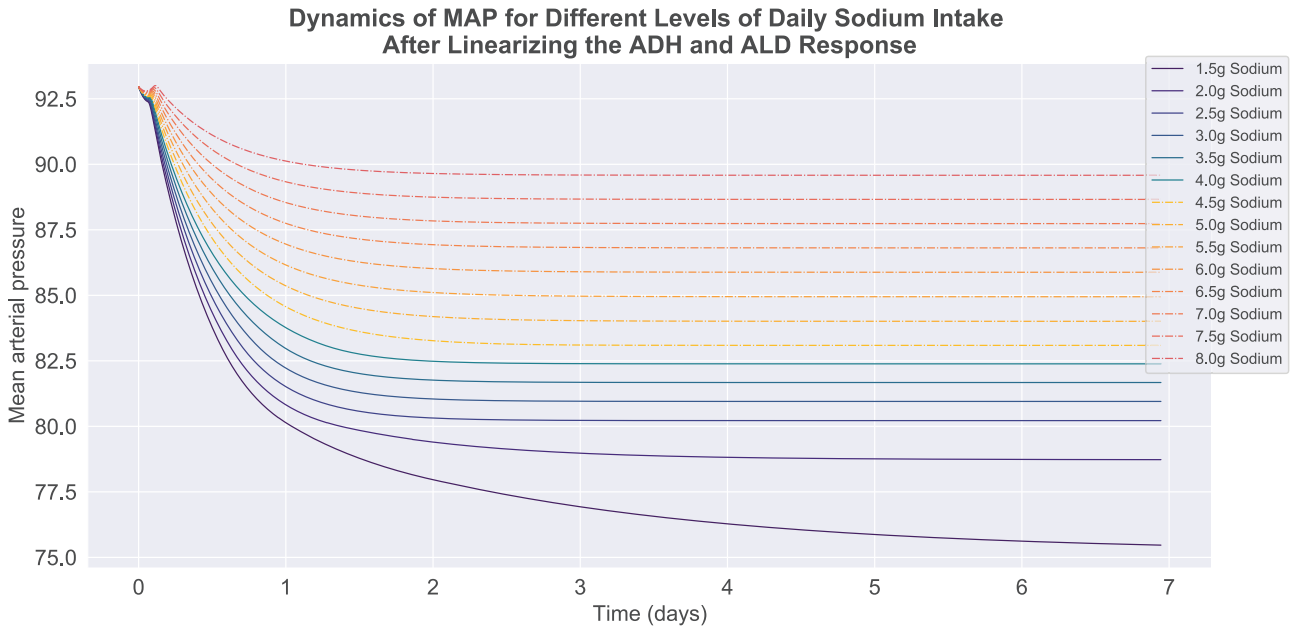

Fig 5. Dynamics of MAP for different levels of daily sodium intake after linearizing the ADH and ALD response. Each color represents the dynamics for a specific daily sodium level, ranging from 1,500 to 10,000 mg/d. The relation between ADH/EBDT is replaced with a 2-segmented linear function as the dashed line plotted in Fig 4A. The relation between ALD/SDTR is replaced with a 2-segmented linear function as the dashed line plotted in Fig 4B. With replaced functions, the MAP in range B cease to converge.

PNA < 135 mEq/L; symptoms include headache, nausea, and poor balance) and the system fails to effectively regulate its total body water within the normal range of ±0.2% of the body mass per day,[32,33] as in Fig 7. At this low end, the simulation cannot reach a steady state, so the MAP values shown here are not to be expected in observation. The results in this domain do not correspond to a relevant physiologic regime under normal human dietary conditions. Therefore, empirical data are absent in formulating the Uttamsingh model for this range. Moreover, results in this range should not be considered to be predictive. Although the use of a model cannot definitely indicate the harm, this anomaly is congruent with the importance of sodium for physiologic functions and is consistent with the claim that extreme low dietary sodium can be hazardous, especially when considering health outcomes beyond blood pressure.[34–36] The uncertain physiologic outcomes in the low range call for further study to expand the understanding of their physiology, and to develop models both for the generic population and for specific individuals.

Discussion

Limitations

This study is subject to the inherent limitations of the modeling methodologies of the Uttamsingh model and HumMod. As noted by Rosenblueth and Wiener,[37] "No substantial part of the universe is so simple that it can be grasped and controlled without abstraction," let alone one of the most complex entities of the universe—the human body. Hence, it is sometimes said, "All models are wrong, but some are useful."[38,39] The available empirical data are insufficient to determine the many parameters of the empirically motivated models we report on, or the overall reliability of those models. These limitations should motivate better approaches to theoretical modeling and a tighter link between empirical studies and theoretical analysis.[40,41] The purpose of this study is not to develop new models or to precisely predict physiologic outcomes or to propose yet another recommendation for sodium intake, but rather to point out the disagreement between the current low-sodium policy and the results from both empirical research and empirically derived mathematical modeling.

Thus, we note that the original Guyton model, the Uttamsingh model, and HumMod are all limited in their own ways. Although the Guyton model has greatly advanced the understanding of the cardiovascular system, some of its fundamental assumptions have been widely debated.[42,43] Validity tests show that it has a relatively poor agreement with empirical observation when simulating the MAP change during the switch from a very low sodium diet to a high one.[44] The Uttamsingh model extended the Guyton model by introducing macula densa sodium flow to adjust rennin flow and provided a more detailed description of some hormonal effects. Similar to the Guyton model, however, the Uttamsingh model underestimates the importance of the nervous system in regulating AP,[45] which is further extended in contemporary models.[46] As for HumMod, in our validity test, simulating with recommended water intake of 2.5 L/d and potassium intake of 90 mmol/d,[25,26] even with a sodium intake as low as the recommended level of 2,300 mg/d, the stabilized plasma sodium concentration in HumMod reaches 150 mEq/L, which is beyond the normal regulation range of 135–145 mEq/L and is considered hypernatremia. Moreover, the system is overly sensitive to potassium intake. For example, increasing the potassium intake to 120 mmol/d (recommended by the U.S. Institute of Medicine[47]) while maintaining other intakes will lead to a stabilized plasma sodium concentration of 156 mEq/L, which is far outside of the healthy range.

We further note that the salt sensitivity may vary based on the individual. The factors include, but are not limited to, race, sex, age, and hypertension.[48–53] In the formulation of the Uttamsingh model, a reference normotensive male of 70 kg was used and physiology measurements (total body water, total body sodium, etc) were set accordingly. Absent comparisons with empirical data, simulation results should not be extrapolated and the simulated optimal intake level should not be viewed as a general guideline.

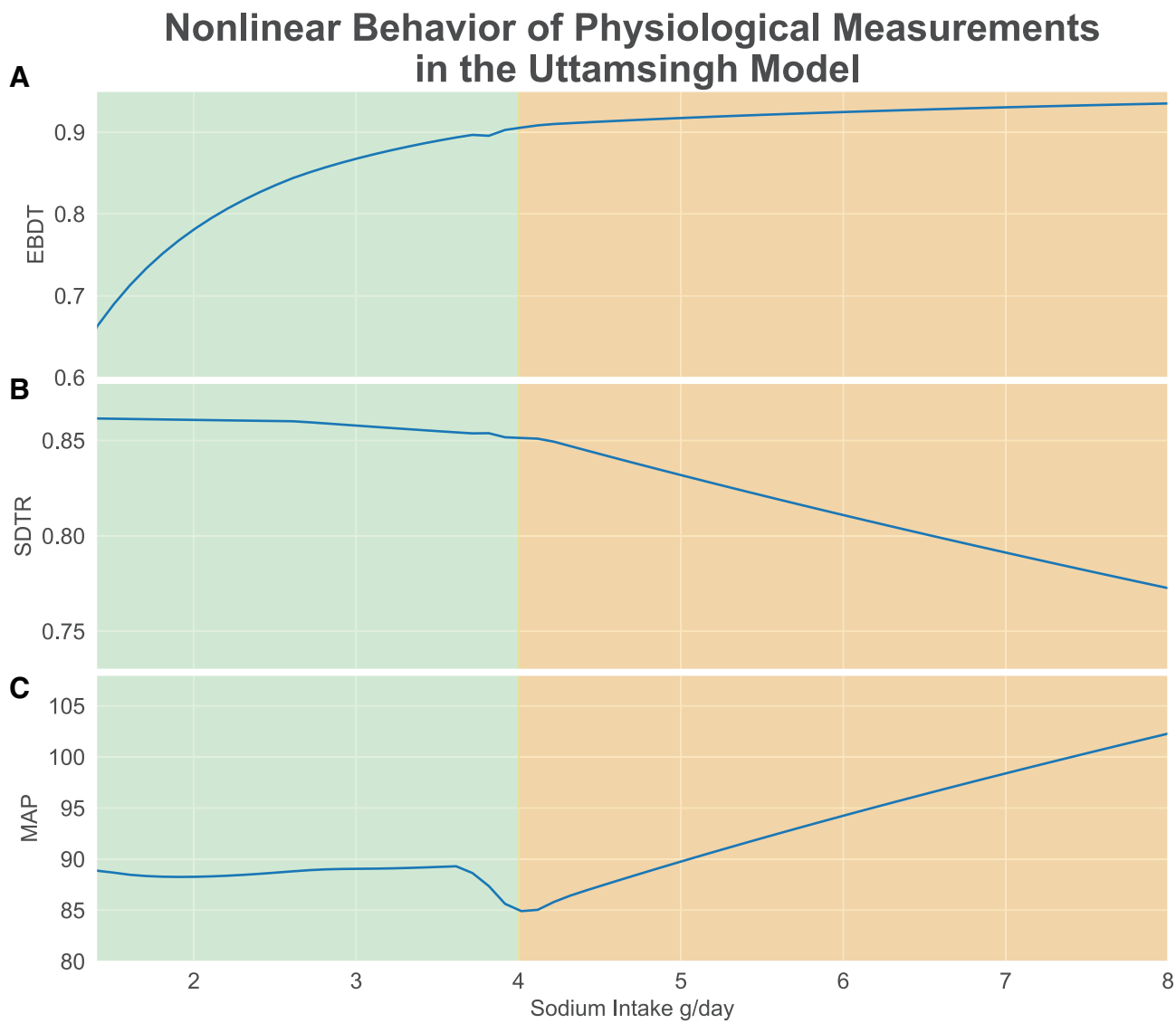

Fig 6. Nonlinear behavior of physiologic measurements in the Uttamsingh model. When water and potassium daily intakes are fixed to the WHO recommendation level, EBDT, SDTR, and AP are all plotted as functions of sodium intake. Different colors are used to label the ranges as previously defined. A and B, The reabsorption ratio of water and sodium is shown. In range B (green area), the system is retaining sodium (high absorption ratio) and excreting water (relatively low reabsorption ratio). In range C (orange area), the system is retaining water but eliminating sodium. C, The stabilized MAP in Fig 2 for comparison is shown.

Conclusions

Based on the Uttamsingh model, for the middle sodium intake range (1,200–4,000 mg/d), the MAP is maintained in a healthy range across the range of intakes. In the higher range (>4,000 mg/d), increasing MAP is associated with increasing sodium intake. The physiologic status in the low dietary sodium range (<1,000 mg/d) remains unclear, but the simulation suggests that the physiologic system can become unstable in this range.

Overall, our simulation supports the U-shape theory of dietary sodium intake, which posits a physiologically stable range for intermediate sodium intake levels, and the potential harm of both low and high sodium intake. Although the literature considers the potential harm of low sodium intake, the frequent advocacy of lower intake should prompt the clearly stated qualification: a dangerously low sodium intake is possible. This is not surprising, given that sodium is an essential nutrient. The value for optimal sodium consumption varies across individuals and activity levels. Nevertheless, it is reasonable to suggest that current recommendations need to be reevaluated. The discrepancy between the recommended levels (1,500 and 2,000 mg/d) and values that lead to the lowest major CVD event rates (approximately 4,300 mg/d) can have several reasons. These include the variance in measuring actual sodium intake (urinary versus dietary), variance in measuring outcome (blood pressure versus cardiovascular event rates), and factors other than sodium contributing to health.[1] Although the high sodium intake range has been shown to be harmful, decreasing intake from the social status quo to the recommendations requires more compelling evidence. Regulatory changes from sodium retention to sodium excretion at approximately 4,000 mg/d suggest an evolutionary optimality. This observation is consistent with both naturally occurring consumption patterns and recent empirical studies.[19,27]

Our result provides a self-consistent picture of the role of sodium regulation and the effect of sodium on overall health. We find that the transition point between sodium retention for low sodium intakes and sodium excretion for high intakes is consistent with the optimal sodium intake levels in empirical studies. The plausibility of this argument does not guarantee its accuracy but points to the opportunity for new research to validate it.

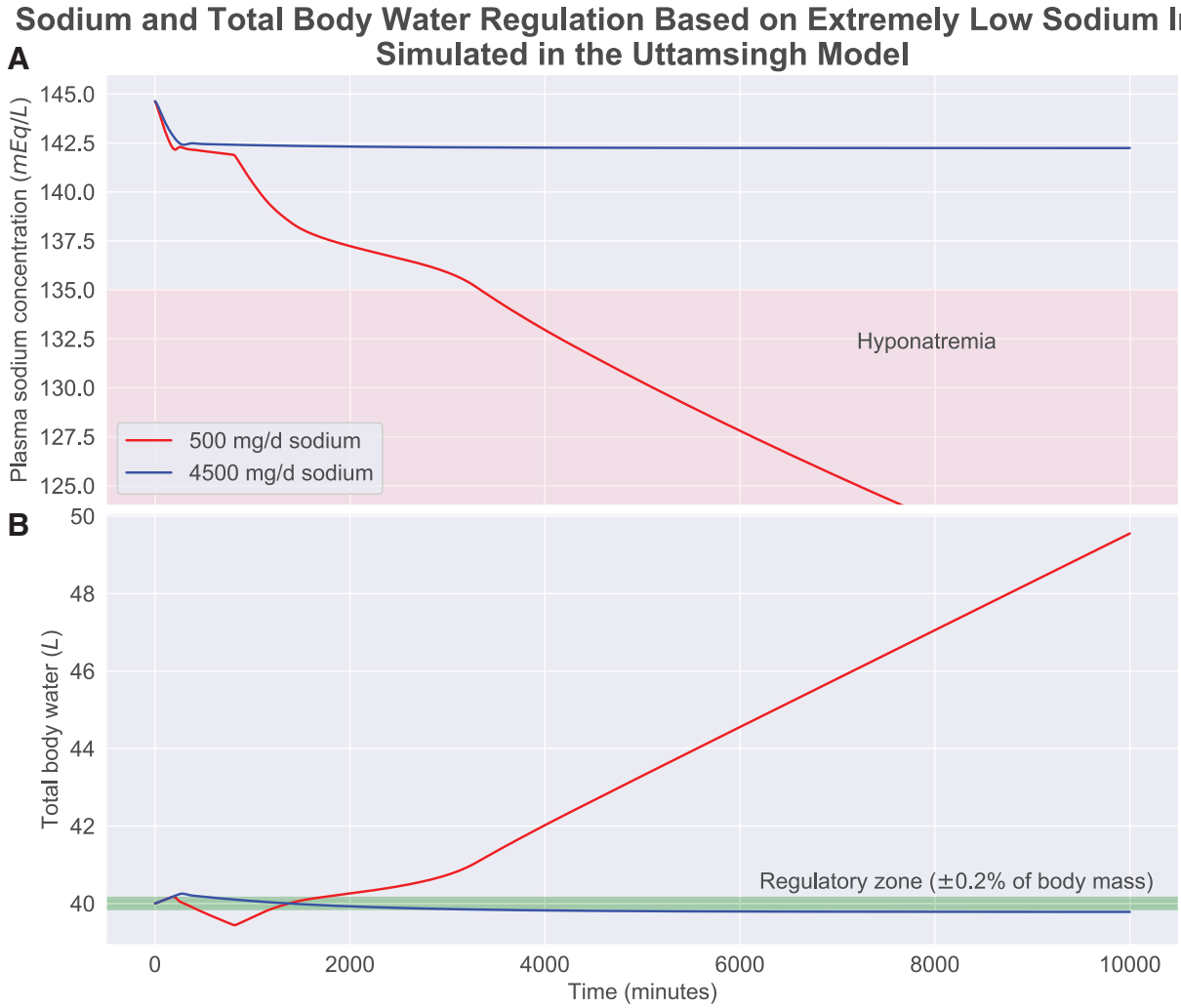

Fig 7. Sodium and total body water regulation based on extremely low sodium intake simulated in the Uttamsingh model. Total body water for sodium intake of 500 mg/d (red curve) compared with sodium intake of 4,500 mg/d (blue curve). A, The dynamics of plasma sodium concentration (PNA) is shown. When falling into the pink range, it is considered hyponatremia. B, The dynamics of total body water, which the system fails to regulate within the normal range of ±0.2% of body mass, is shown. Because of the limitations of empirical data used in constructing the Uttamsingh model, these results should not be considered to have predicative utility but rather to motivate additional empirical and theoretical efforts.

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