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# A 5-component mathematical model for salt-induced hypertension in Dahl-S and Dahl-R rats

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ABSTRACT

Salt-induced hypertension has been demonstrated in a variety of species including rats, monkeys, chimpanzees and humans. Until recently, the multiple phases of this blood pressure increase due to high salt intake had not been closely studied. This work builds upon a recent study, which developed a grey-box multi-component model of salt-induced hypertension in the Dahl-S rat. The previous 3-component model has been extended here to include additional model dynamics to improve the model fit and add new important elements to the model response. The model was optimised using numerical techniques with experimental data from 4 different protocols with Dahl-S, Dahl-R and FF2 hybrid rats. Results show a marked improvement over the previous model and confirm the merit of the 5-component model structure. A comparison between the model dynamics for different rat strains has also been included.



## 1. Introduction

Salt-induced hypertension (SIH) is a process whereby a subject develops high blood pressure (BP) due to high salt intake and individuals can be categorised into salt-sensitive or salt-resistant [1,2]. Salt intake has often been linked to the development of hypertension [3–5] and the BP response to salt has been studied in chimpanzees [6], spider monkeys [7], rats [8,9], mice [10] and humans [11].

Until recently, salt-induced hypertension was viewed as a single event and different time courses of the development of hypertension were not distinguished. This was mainly due to a lack of long term data sampled at short enough intervals to determine different phases of the response. Van Vliet et al. [12] first emphasised the presence of two distinct phases of SIH in Dahl salt-sensitive (Dahl-S) rats and, in addition, their study showed that similar effects were also present to various extents in hybrid rats.

Based on this idea, and using the same experimental data, a multi-component grey-box model was created to simulate the acute and progressive time-courses in BP increase due to high salt intake [13]. The model comprises three dynamic components, as shown in Fig. 1, and was optimised for both Dahl salt-sensitive and hybrid rats. The model was shown to fit the data reasonably well and possible physiological explanations were assigned to each component. A major drawback, however, is the inability of this 3-component model to account for certain features present in the experimental data.

In the present study, the existing 3-component model is extended to improve the data fit and assign a model structure that is possibly more representative of the underlying physiological system. Two new model components were developed using the average data for each experimental protocol (i.e. the

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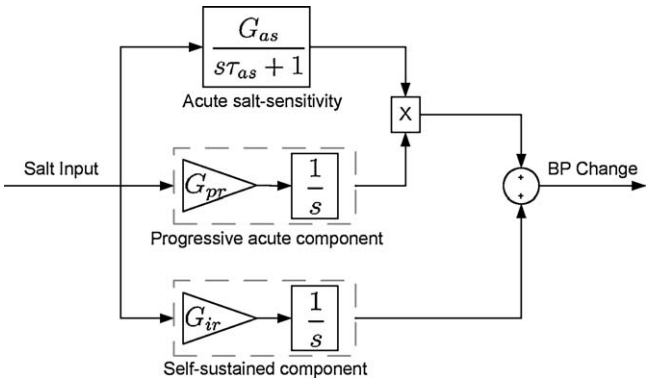


**Fig. 1 – 3-Component model structure developed in [13]**

'mean animal'), as it is relatively noise-free data and emphasises features present in most if not all animals within a data set. Subsequently, the models were parameterised for each individual animal, including control Dahl salt-resistant (Dahl-R) animals. Chronic pressure–natriuresis relationships were also plotted for various animals to demonstrate the different features in the progression of SIH.

The remainder of the paper is organised as follows: Section 2 gives a brief overview of the data sets used in this study and Section 3 shows the model structure development. Section 4 describes the numerical techniques employed for model parameter optimisation, while Sections 5 and 6 present the results and discussion of the work.

## 2. Experimental data

Data from four different experimental protocols were used in this study. Plots of the 'mean animal' data for each protocol as well as the respective salt inputs are shown in Figs. 2 and 3.

### 2.1. *Protocol 1*

Experimental protocol 1, described in detail in [12], was conducted on nine 3-month-old male Dahl-S rats from the Brookhaven strain. A step increase in dietary salt intake was applied for 6 weeks (4% NaCl), followed by a 4-week recovery period with normal salt intake (0.7% NaCl). Blood pressure was recorded using telemeters at a rate of a sample per minute. The 24-h average mean arterial pressure (MAP) was used in the study. A separate set of seven Dahl-R rats were used as control subjects and were fed the same diet as the Dahl-S rats. Fig. 2 shows a plot of the 'mean animal' for the Dahl-S and Dahl-R rats and the associated salt intake.

### 2.2. *Protocol 2*

Protocol 2 was designed to investigate the reversibility of salt-induced hypertension and was reported in [12]. The protocol included variations in salt intake during a course of eleven weeks. The subjects were five male Dahl-S rats, instrumented with telemeters for blood pressure recording. Weeks 1, 3, 7 and 11 included normal salt diet of 0.7% NaCl, while during weeks 2, 4–6 and 8–10 the animals were given high salt diet of 4% NaCl. Fig. 2 shows a plot of the 'mean animal' and salt intake for this protocol.

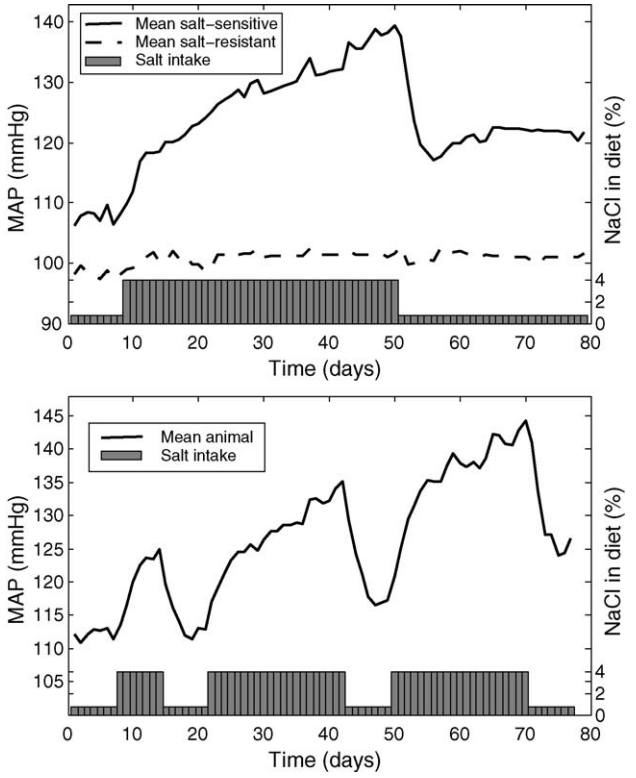


**Fig. 2 – 'Mean salt-sensitive' and 'mean salt-resistant' animals of Protocol 1 (top) and 'mean salt-sensitive' animal of Protocol 2 (bottom) and associate salt intake levels.**

### 2.3. *Protocol 3*

Protocol 3, described in [13], investigates the effect of short-term changes in salt intake on the daily MAP level of eight male Dahl-S rats and five control male Dahl-R rats . The salt levels in the diet were varied in a pseudo-random binary sequence where, at each day of the experiment, the level of salt was either changed or it stayed the same. BP telemeters were implanted in all rats and a recovery period was allowed before a high salt diet was given. The protocol was 72 days long and the daily mean BP level was calculated as the average level of MAP sampled once each minute. The dietary salt level was manipulated in the following manner, 0000000001 1111101010 1100110111 0110100100 1110001011 1100101000 110000100000, with each '0' representing a 24 h exposure to a regular salt diet (0.7% NaCl) and each '1' indicating a 24 h exposure to high salt diet (4% NaCl). Fig. 3 shows a plot of the 'mean animal' for the salt-sensitive and salt-resistant rats, in addition to the salt intake levels.

### 2.4. *Protocol 4*

Protocol 4, described in detail in [12] and similarly to Protocol 1, was conducted to study the BP response to a step increase in salt level in the diet of rats. Thirteen male FF2-hybrid rats (progeny of the cross between Dahl-S and Dahl-R rats) were