33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Modeling the Adaptive Pathophysiology of Essential Hypertension

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***Abstract*—This paper proposes an adaptive neuro-fuzzy model to study the pathophysiology of essential hypertension. Using diverse inputs such as risk factors, physical relations and medical interventions, and states that include both transient and resting states for key physiological variables (blood pressure, total peripheral resistance), it can roughly predict both real-time and long-term blood pressure change for a robust range of inputs. Although it was tuned using published population data, it can be applied to specific individuals to estimate the risks of hypertension with different life experience.**

I. Introduction

HYPERTENSION, an abnormally elevated blood pressure (BP) typically associated with resting arterial BP, is a risk factor for many diseases, including stroke and myocardial infarction. In the United States it has been estimated that hypertension affects about 25% of adults, and the prevalence of hypertension increases with advancing age to the point where more than half of people 60–69 years of age and approximately three-fourths of those 70 years of age and older are affected [1].

The etiology of hypertension remains a research challenge, especially given that BP can fluctuate considerably over the course of a day [2]. A small number of patients (between 2% and 5%) have an underlying renal or adrenal disease as the cause for their raised BP. In the remainder, however, no clear single identifiable cause is found and their condition is labeled "essential hypertension."

Medication can temporarily lower BP and help prevent complications. However, medications do not attack the source of the problem [3], even if they do lower risks. BP can change due to lifestyle stressors, and part of the intervention strategy involves lifestyle modifications. Put together, an incomplete picture emerges, especially as related to the dynamics of slower, adaptive changes that include cardiovascular tissues. This paper presents a dynamic model of hypertension, operating on both "real-time" and adaptive time scales, that can be used to help elucidate some of the underlying mechanisms and to help predict risks.

II. Background

The key physical factors that affect the BP are the total peripheral resistance (TPR) of the vascular network, the cardiac output (CO), and the blood volume (BV). The TPR is determined by the physical properties (such as radius and stiffness) of the vascular network and controlled by central neural system through vasoconstriction and vasodilation. The CO is mathematically the product of heart rate (HR) and the stroke volume (SV). For a given TPR, the higher the cardiac output, the higher the arterial BP. A key strategy for lowering BP is to provide medications that vasodilate vessels by decreasing smooth muscle tone, typically by lowering the sympathetic drive. The BV is a function of osmotic pressure, which in turn is especially influenced by the concentration of sodium. Compared to possible changes in TPR and CO, changes in blood volume occur more slowly, but play a very important role in long-term BP regulation.

The pathology of essential hypertension remains unknown, although it is widely agreed that sodium and water balance play a role, as does the general state of vasoconstriction within the arterial network. Risk factors include genetic effect, age, obesity, physical inactivity, tobacco usage, alcohol usage, and stress [1]. Another hypothetical pathology of essential hypertension is rooted in the concept of allostasis, defined as "the continuous process of adaptation that the host undergoes in the face of potentially stressful challenges … by which an organism achieves internal viability through a bodily change of state" [3]. The idea is that a sustained demand for elevated BP causes gradual adaptation: arterial smooth muscle cells hypertrophy; the carotid sinus wall thickens to reduce baroreceptor sensitivity; and secretory cells whose products support the BP rise increase their production rate (renin, norepinephrine, cortisol, etc.).

Besides drugs and proper diet (including reducing salt intake and cholesterol intake) [1], regular aerobic exercise is also recommended to hypertension patients [4], with long term anti-hypertensive effects of exercise mostly considered to be due to a reduction in TPR [5], including an initial short term reduction in BP following a bout of acute exercise, which is also called post-exercise hypotension (PEH).

III. Method

This paper uses a rule-based modeling framework based on fuzzy logic and conceptually implemented as a neural network [6]. This model is composed of inputs, states, and outputs. Fuzzy rules are used to establish causal relationships between inputs and states. By using fuzzy rules to create causality that results in nonlinear differential equations, it is a platform which can capture the dynamic changes in states, assuming the user provides the causal relationship between inputs and states (e.g., based on research evidence and/or consensus expert knowledge). The fuzzy rules are dimensionless, and parametric scaling is normally associated with the output equations that are implemented at each time step after integration of the state variables.

A. Inputs

The inputs in this model are those environmental factors which: *i)* can cause changes in BP regulation, such as exercise and drugs; or *ii)* irreversible conditions that affect

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the resting BP, such as the aging process and genetic factors. The inputs are determined from evidence found in scientific publications, and only factors whose individual effect can be identified are adopted as inputs. Some risk factors of hypertension are also included as inputs, demonstrating the robustness of the neurofuzzy approach.

TABLE 1. Inputs

Age	(0,120) in years.
GeneRisk	Degree of "bad genes" (0,1), 1 means highest risk.
Stress	Stress environment during daily life over time durations, (0, 10); 10 means the most stressful environment (e.g., extreme score in stress tests)
Exercise	Bout of aerobic exercise, defined by an intensity (0, 10); 10 is maximum oxygen uptake and time duration.
NaInTake	Daily salt intake, (0, 300) mmol per day (the U.S. recommended amount is less than 100 mmol/day).
Diet	The diet plan, (0,1); 0 means the most healthy diet and 1 means the worst. The value for DASH (Dietary Approaches to Stop Hypertension) diet is assumed 0.05.
Medication	One *ACE-inhibitor* (ramipril) and one diuretic (HCTZ) were selected as demo (more drugs can be added).
BPDifference	The difference between the real time BP and resting mean BP; it is actually a feedback from the outputs.

B. States

There are two BP-related states in this model: resting mean BP (RestBP) and real-time mean BP (BP). Accordingly, there are two parts of TPR and heart rate (HR) that correspond to each blood pressure state. Normally RestBP changes slowly in days to weeks, and is affected by TPRrest (the TPR at rest, mainly determined by the mechanical properties of blood vessels) and HRrest, while BP changes in seconds to minutes and is affected by TPRnh (the neural/hormonal regulation induced TPR change during exercise, stress, or drugs) and HRnh (the neural/hormonal regulation induced HR change during exercise, stress, or drugs). Table 2 provides the states. Their ranges were very wide to fit extreme conditions (all states are normalized to [0, 1]). However, by using membership functions that saturate before extremes, a subset of the range is operationally used for most simulation studies.

TABLE 2. States (normalized)

RestBP	Resting mean blood pressure. (0, 220) mmHg.
BP	Real time mean blood pressure. (0, 220) mmHg.
TPRrest	Total peripheral resistance at rest. (0, 0.1) mm Hg/(ml/min).
TPRnh	Total peripheral resistance change caused by neural/hormonal regulation, with the TPRnh value at rest normally set as 0.5.
HRrest	Heart rate at rest, (1, 200) beats/min.
HRnh	Heart rate change caused by neural/hormonal regulation, with the value at rest normally set 0.5.
SV	Stroke volume. (0, 180) ml.
BV	Blood volume. (0, 10000) ml.
Risk	The risk of hypertension at the certain age in the rest of the life (or lives for population data).
Ramiprilat	The plasma concentration of ramiprilat, the effective form of ramipril, with 1 representing 170 nanomoles/liter.

C. Outputs

Most outputs are variables that are direct mapping from the corresponding unnormalized states, including RestBP, BP, TPRrest and HRrest. Another output is the predicted risk of hypertension (a mapping of the state Risk).

TABLE 3. Fuzzy rules*

Left (If) part	***Right (Then) part***
Blood Pressure Rules (real time):	
(TPRnh is High) **AND** (BP is NOT VERY High)	(BP is Higher)
(TPRnh is Low) **AND** (BP is NOT VERY Low)	(BP is Lower)
(HRnh is High) **AND** (BP is NOT VERY High)	(BP is Higher)
(HRnh is Low) **AND** (BP is NOT VERY Low)	(BP is Lower)
(BV is High) **AND** (BP is NOT VERY High)	(BP is Higher)
(BV is Low) **AND** (BP is NOT VERY Low)	(BP is Lower)
(SV is High) **AND** (BP is NOT VERY High)	(BP is Higher)
(SV is Low) **AND** (BP is NOT VERY Low)	(BP is Lower)
RESTING Blood Pressure Rules (slow adaptive):	
(TPRrest is High) AND (RestBP is NOT VERY High)	(RestBP is Higher)
(TPRrest is Low) AND (RestBP is NOT VERY Low)	(RestBP is Lower)
(HRrest is High) AND (RestBP is NOT VERY High)	(RestBP is Higher)
(HRrest is Low) AND (RestBP is NOT VERY Low)	(RestBP is Lower)
(BV is High) AND (RestBP is NOT VERY High)	(RestBP is Higher)
(BV is Low) AND (RestBP is NOT VERY Low)	(RestBP is Lower)
(Diet is Healthy) AND (RestBP is NOT Low)	(RestBP is Lower)
(Diet is Unhealthy) AND (RestBP is NOT High)	(RestBP is Higher)
Total Peripheral Resistance (TPR) Rules (3 resting):	
(Stress is High) **AND** (TPRnh is NOT High)	(TPRnh is Higher)
(Exercise is High) **AND** (TPRnh is NOT Low)	(TPRnh is Lower)
(Ramiprilat is High) **AND** (TPRnh is NOT Low)	(TPRnh is Lower)
(Age is Old)	(TPRrest is Higher)
(TPRnh is Low)	(TPRrest is Lower)
(BPDifference is PositiveHigh)	(TPRrest is Higher)
Cardiac Output (CO) Rules:	
(Stress is High) **AND** (HRnh is NOT High)	(HRnh is Higher)
(Exercise is High) **AND** (HRnh is NOT High)	(HRnh is Higher)
(Exercise is High) **AND** (SV is NOT High)	(SV is Higher)
BV Rules	
(NaIntake is High) **AND** (BV is NOT High)	(BV is Higher)
(NaIntake is Low) **AND** (BV is NOT Low)	(BV is Lower)
($Conc_{HCTZ}$ is High) **AND** (BV is NOT Low)	(BV is Lower)
Other	
(GeneRisk is High) **OR** (RestBP is High)	(Risk is Higher)
($Conc_{Ramipril}$ is High) **AND** (Ramipril is NOT High)	(Ramipr. is Higher)

*: The left side contains inputs and states, and right side how states change. Within parenthesis is the degree that an input or state is a membership function associated with the respective input or state variable, and the consequent of each operation is a degree of "membership" between 0 and 1.

D. Fuzzy rules (Table 3)

Fuzzy rules related to real time BP: The real-time mean BP is assumed to be affected by TPRnh, HRnh, SV, and BV. The rules related to BP are 4 causal pairs that reflect the basic physical relationships, with BP a function of four other states.

*Fuzzy rules related to **resting** BP:* The resting mean BP is affected by TPRrest, HRrest, SV, and BV. The rules related to resting BP are 4 causal pairs that reflect physical relationships between states. Other factors affect resting BP, such as diet, are also provided to illustrate the capabilities of this model.

Fuzzy rules related to TPR: The short-term change of TPR is through vasoconstriction and/or vasodilation, which is controlled by neural and humoral factors. The long term change of TPR is due to the change of mechanical properties of blood vessels, i.e., hypertrophy of smooth muscles in vessel wall, which is caused by the adaptation of the smooth muscle to mechanical loads [7]. In the aging process, arteries become thicker, stiffer, and less flexible [8], which is assumed to cause a relatively higher TPR. Some medications may also prevent increases in TPR.

Fuzzy rules related to CO: The change of CO is caused by changes in heart rate or stroke volume or both. The most common event causing CO change is exercise, with the healthy adult resting CO of about 5L/min increasing during intense exercise to over 20L/min, while the HR can double or even triple. SV also increases with exercise intensity.

Fuzzy rules related to blood volume: The short-term change of blood volume (e.g., bleeding and transfusion) is not involved in the pathogenesis of hypertension and hence not included in this model. The long-term change of blood volume is related with the change of the setpoint of sodium.

Fuzzy rules related to Risk: The risk of hypertension of a healthy person within a population depends on genetic and environmental factors. The former can be analyzed from the family health history, and the latter is a reflection of the integrated effects such as exercise, stress, life style, etc.

Other rules: There is another rule that relates to the pharmacokinetics of Ramipril.

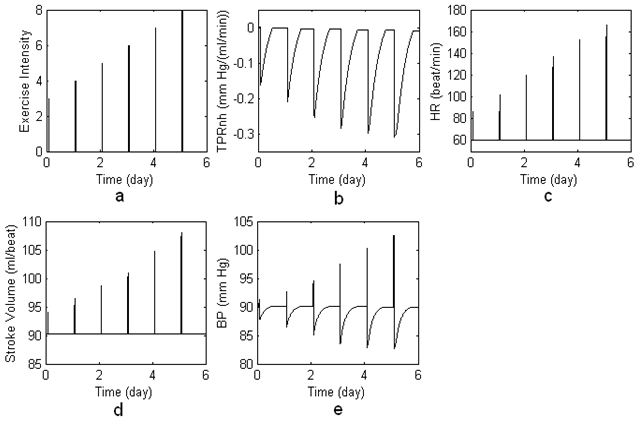

Fig. 1. Model response of cardiovascular system during aerobic exercise. (a) Input of aerobic exercise, once per day, 30 min per session, with intensity of 30% of VO2max in the first day, increased gradually to 80% the sixth. (b) Predicted change in TPR, showing a sharp decrease during an exercise event followed by a more gradual change back to a base level. (c) Change in HR, showing increases as a function of exercise intensity. (d) Predicted change in stroke volume. (e) Predicted change in mean BP, showing an increase during exercise followed by a temporary decrease.

IV. RESULT

A. Real-time model predictions

Effect of exercise: In the simulation of Fig 1, the assumed scenario is that a healthy person performing several bouts of endurance exercise. The changes of HR, TPRnh, BP, SV during exercise and the post-exercise hypotension effect are consistent with available evidence [9].

Effect of diet and sodium intake: The simulation of Fig 2a and 2b is based on the study of DASH collaborative research group [10] involving 459 adults, where for three weeks, subjects were fed a control diet (low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States), then were randomly assigned to an 8-wk trial of one of the following (controlled for sodium): 1) a control diet; 2) a diet rich in fruit and vegetables (the Vege diet); or 3) a combination diet with reduced saturated and total fat (the DASH diet). The model was optimized by tuning parameters: Inputs\Diet\MF\Healthy\ShapeFactor and Inputs\Diet\MF\Healthy\SensitivePoint.

The effect of Na intake on BP, as shown in Figure 2c and 2d, is based on two randomized clinical trials: an 8-week Australian National Health & Medical Research Council Dietary Salt Study (88 controls; 44 experimental in an Na intake group receiving less than 80 mmol Na daily in the diet plus 80 mmol of Na supplement; 44 receiving less than 80 mmol Na daily in the diet plus placebo tablets daily) [11], and DASH-Sodium collaborative research group (204 participants, diets with three different Na levels, in random order) [12]. The neurofuzzy model was optimized by tuning the parameters Inputs\NaIntake\MF\Healthy\ShapeFactor and Inputs\NaIntake\MF\Healthy\SensitivePoint.

The combination of diet and low Na intake has greater effect (about 6 mm Hg reduction in mean resting BP) on BP control than individual DASH (4.25 mm Hg) or low Na intake (5.1 mm Hg), as Fig 3e shows. However, the predicted total effect of two therapies is less than the sum of the individual ones.

Effect of stress: The response of BP to stress is shown in Fig 3a, which is the simulation result of the change of mean BP caused by a bout of stress. As a response to an event of one-hour stress with intensity of 6, the mean BP increased about 19 mm Hg, which is consistent with evidence [13].

B. Longer-term Adaptive Model Predictions

Aerobic exercise and stress: One predicted consequence of the acute response of BP to different intensity of endurance exercise (Fig 1) is that due to residual vasodilation, the post-exercise TPR transiently drops for hours. This may help explain the beneficial effect of long-term endurance exercise on BP. For example, the cross-sectional compliance of large arteries in cyclists is significantly higher than that in sedentary subjects, which suggests endurance training might cause structural adaptation in muscle tone of muscular arteries [14]. As Figures 3b-c show, a longer-term simulation run with the model predicts that with a 2-year stressful lifestyle (1 hour/day of intensity of 8) the mean resting BP escalates about 10 mm Hg. However, also shown overplotted are model predictions of the anti-hypertensive effect of adding long-term regular endurance exercise to help compensate for such stress, an effect that in the model results mainly from preventing the raise of TPR, though even with exercise, the mean resting BP still increases a little bit due to increased TPRrest (Fig 3b), which is a consequence of another input - the aging effect on blood vessels (e.g., changes in collagen content).

Risk of hypertension: Key risk-related model parameters were tuned primarily through population data from various studies, with the risk of hypertension of a given subject depends on three main factors (genetic factors, age, and life experience). The model predictions of the long-term effect of age and life experience as risk factors of hypertension are in Fig 2f and 3c. Fig 4 shows the model prediction of the risk of hypertension due to the aging process alone and when combined with high genetic risk. Note that the model was tuned using other data, and is now being used with novel inputs. This demonstrates how the model makes predictions that appear fairly robust, given a novel input scenario. This could form the basis for new studies that test such predictions.

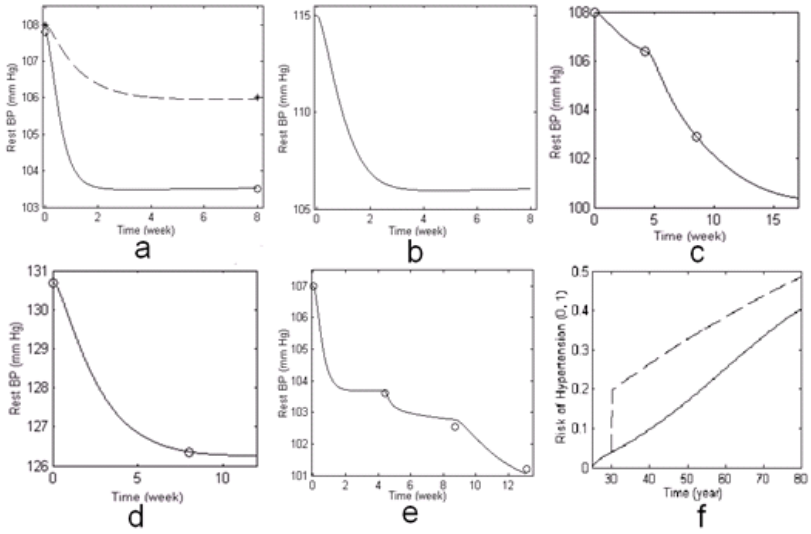

Fig. 2. The effect of diet and low sodium intake on blood pressure control. o and *: measured data. Solid line and dash line: simulation result. (a) 8 wk diet [10]. o and solid line: DASH diet. * and dash line: Vege diet. (b) The predicted effect of 8-wk DASH diet on hypertensive subjects (mean resting BP 115 mm Hg). (c) The effect of Na-intake on blood pressure, starting at high level Na, then intermediate, followed by low level [11]. (d) Australian dietary salt study [12]. (e) The combination effect of both diet and low Na intake on blood pressure control in subjects (mean resting BP 107 mm Hg) with 90-day DASH diet. The Na intake level is 30-day high followed by 30-day intermediate, and 30-day low. (f) The risk of hypertension due to age, Na intake and diet. The model simulation is the predicted risk of hypertension of a healthy 25 years old male until he is 80. Initial Na intake: 130 mmol/day. Initial diet level: 0.4. After age 30, Na intake: 160 mmol/day. Diet level: 0.6. Solid line: the risk of hypertension due to aging process. Dash line: the risk of hypertension due to aging process and excessive Na intake and unhealthy diet. The dash line and solid line overlap from age 25 to 30.

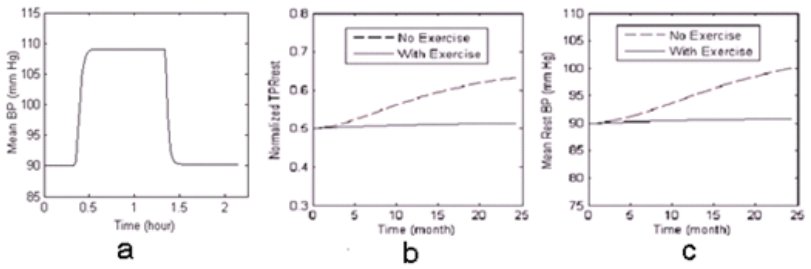

Fig. 3 BP responses to stress. (a) BP change due to a bout of stress. The initial mean blood pressure is 90 mm Hg, the input is a one-hour stressful event with intensity 6. (b) and (c) Long-term effect of BP response to stress and exercise. The assumed scenario is that a healthy male (initial mean rest BP: 90 mm Hg) undergoes a stressful life (one-hour stressful environment with intensity of 8 every day) for 24 months, with or without exercise. Solid line: 30-minute endurance exercise at 70% of VO2max every day. Dash line: no exercise. (b) Predicted normalized TPRrest. (c) Predicted mean resting blood pressure.

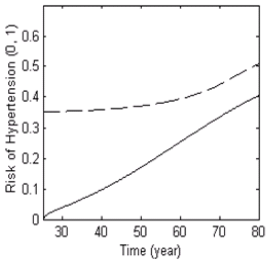

Fig. 4. The risk of hypertension due to aging and genetic influence. The model simulation is the predicted risk of hypertension of a healthy 25 years old male until he is 80. Na intake: 130 mmol/ day. Diet level: 0.4. Solid line: without hypertensive parent, the risk of hypertension due to aging process. Dash line: with one hypertensive parent, the risk of hypertension due to aging process and genetic influence.

V. CONCLUSION

This paper presents an integrated neuro-fuzzy model to study the pathology and treatment of hypertension. Tuned by population data from available studies, it can predict the basic effects of endurance exercise, sodium intake, diet, drugs, aging, and genetic factors on BP control. By including nearly all environmental factors whose effects on BP have been identified, it can be used to predict effects of combined therapies that can be evaluated through new studies. Although this model was built for human subjects, it can be applied into an animal model if parameters are justified, because the logic (the causal relationship between the inputs and states) in this model applies for both human and animal subjects.

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