

## Thermodynamic Assessment of Multiple Physiological Stress Responses Using Maxwell Relations

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### ABSTRACT

The present study introduces a macroscopic thermodynamic methodology to quantify entropy change in a human physiological system using Maxwell relations. This approach combines three physiological measures (mean arterial pressure, heart rate, and finger skin temperature) to provide a measure of entropy change ( $\Delta S$ ). The experimental data was collected from a study that included eighty-two subjects (49 males and 33 females). The three physiological measures were taken under three conditions (relaxation, stressor task, and recovery) during the physiological test profile. The entropy change ( $\Delta S$ ) is computed using Maxwell relations in terms of measurable mean arterial pressure, heart rate, and skin temperature. The average values of the physiological responses ( $n=49$  males and  $n=33$  females) are used in the modified Maxwell relations to compute the entropy change from relaxed state to stressor and recovery states for male and female subjects respectively. The results demonstrate that stressor task and recovery do have an impact on human physiology, which is indicated in entropy change values. The entropy change characterizes the human body from a thermodynamics viewpoint and could be valuable for the study of human physiology.

**Keywords** - entropy change; human physiology; Maxwell relations; stress; thermodynamics.

### 1. INTRODUCTION

Numerous studies have been conducted by researchers to apply thermodynamics to model and investigate human physiology. Earlier work done one by Schrodinger [1] establishes the fact that the human life processes are indeed thermodynamic in nature and hence thermodynamic laws can be used to model human physiology. Nicolis and Prigogine [2] have applied the second law of thermodynamics to model open living systems and thereby derived an expression for entropy generation. The earlier studies by Iberall et al. [3-5] have demonstrated the utility of thermodynamics to model integrated dynamics of human physiology. Harold Morowitz [6] has indicated that the knowledge of the biological state without an energetically significant measurement would lead to a violation of the

second law of thermodynamics. It has been hypothesized by Bridgman [7] that the laws of thermodynamics are intrinsically positioned to model the physiological behavior of living systems. The most recently discovered thermodynamics-based Constructal Theory, developed by Adrian Bejan [8, 9] has been used to model pulsating transport phenomena in biological systems Magin et al. [10]. Recently, in studies conducted by Silva et al. [11, 12], entropy generation and human aging are examined using nutritional and physical activity data. Ichiro Aoki [13, 14] has measured entropy flow and production in basal and exercising conditions. Most of these past studies have made significant efforts to apply laws of thermodynamics to study living systems, but none of them have utilized Maxwell relations to combine multiple human physiological responses to measure entropy change. In this regard, the studies conducted by Boregowda et al. [15-17] and Palsson et al. [18] have presented the development and preliminary verification of a physiological entropy change. The purpose of this study is to model human physiological system on a macroscopic as a simple system using Maxwell relations.

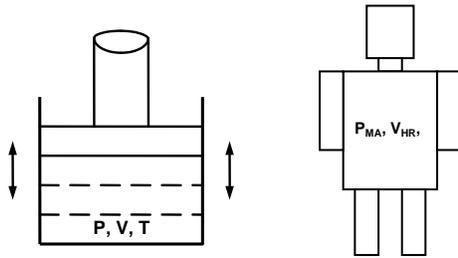
### 2. MODELING AND FORMULATION

The modeling is based on the idea that Maxwell relations can be used to calculate entropy change in terms of measurable physical quantities such as pressure, volume, and temperature [19, 20]. An analogy between physical and human physiological systems is conceptualized and the properties of a non-living system are mapped to that of a living system as shown in Table 1 and Figure 1. The physical system characterized by pressure (P), volume (V), and temperature (T) are mapped to that of a human system - mean arterial pressure ( $P_{MA}$ ), heart rate ( $V_{HR}$ ), and skin temperature ( $T_s$ ), respectively.

#### 2.1 Assumptions

(a) Human physiological stress response system is considered as a simple system from a macroscopic perspective for the purpose of this study. This makes it possible to apply Maxwell relations to examine human physiology from a thermodynamics perspective.

(b) Mean arterial pressure, Heart rate, and Skin temperature are equivalent to Pressure, Volume, and Temperature, respectively as shown in Fig. 1.



**Entropy (S) = f (P, V, T)    Entropy (S) = f (P<sub>MA</sub>, V<sub>HR</sub>, T<sub>S</sub>)**

**Figure 1. Similarity analysis of simple mechanical and human physiological systems**

(c) The heart rate is an indirect measure of stroke volume of blood in the heart region and is thus used in the place of stroke volume. Please note that heart rate (in beats per minute) is equal to cardiac output (mL/min) divided by stroke volume (mL/beat).

(d) The ratio of partial changes in two physiological variables is accompanied by constancy in the third variable as this is the basis of Maxwell relations. For example, when there is a partial change in heart rate with respect to partial change in entropy, the mean arterial pressure remains constant.

**Table 1: Comparing Two Simple Systems: Mechanical and Human**

Physical Variables (Simple Mechanical System)	Physiological Variables (Simple Human System)
Pressure (P)	Mean Arterial Pressure (P <sub>MA</sub> )
Volume (V)	Heart Rate (V <sub>HR</sub> )
Temperature (T)	Skin Temperature (T <sub>S</sub> )
Entropy (S)	Physiological Entropy (S <sub>P</sub> )

**2.2 Derivation of Physiological Entropy Change**

Let us begin with mathematics by considering a variable z that is a continuous function of x and y (Callen, 1985).

$$z = f(x,y) \tag{1}$$

It is convenient to write the above equation in the following form:

$$dz = M dx + N dy$$

Where  $M = (\partial z / \partial x)_y$  ;  $N = (\partial z / \partial y)_x$

If in Eq. (1), x, y, and z are all point functions (i.e., quantities that depend only on the state and are independent of the path), the differentials are exact differentials. Therefore, in order for Eq. (1) to be an exact differential equation, the following condition must be satisfied:

$$(\partial M / \partial y)_x = (\partial N / \partial x)_y \tag{2}$$

Eq. (2) is called the Exactness Condition.

Maxwell relations are derived from the property relations of thermodynamic potentials by invoking the exactness condition. For a simple human physiological system, there are four thermodynamic potentials:

- Internal Energy:  $dU_P = T_S dS_P - P_{MA} dV_{HR}$
- Enthalpy:  $dH_P = T_S dS_P + V_{HR} dP_{MA}$
- Helmoltz Function:  $dA_P = -P_{MA} dV_{HR} - S_P dT_S$
- Gibbs Function:  $dG_P = V_{HR} dP_{MA} - S_P dT_S$

The following Maxwell relations are obtained by invoking the exactness condition on the above four property relations:

$$(\partial T_S / \partial V_{HR})_{S_P} = -(\partial P_{MA} / \partial S_P)_{V_{HR}} \tag{3a}$$

$$(\partial T_S / \partial P_{MA})_{S_P} = (\partial V_{HR} / \partial S_P)_{P_{MA}} \tag{3b}$$

$$(\partial P_{MA} / \partial T_S)_{V_{HR}} = (\partial S_P / \partial V_{HR})_{P_{MA}} \tag{3c}$$

$$(\partial V_{HR} / \partial T_S)_P = -(\partial S_P / \partial P_{MA})_{T_S} \tag{3d}$$

The above-mentioned partial derivatives are approximated to form a modified set of Maxwell relations that are used in the present experimental study to compute the physiological entropy change:

$$(\Delta T_S / \Delta V_{HR})_{S_P} = -(\Delta P_{MA} / \Delta S_P)_{V_{HR}} \tag{4a}$$

$$(\Delta T_S / \Delta P_{MA})_{S_P} = (\Delta V_{HR} / \Delta S_P)_{P_{MA}} \tag{4b}$$

$$\Delta P_{MA} / \Delta T_S)_{V_{HR}} = (\Delta S_P / \Delta V_{HR})_{P_{MA}} \tag{4c}$$

$$(\Delta V_{HR} / \Delta T_S)_{P_{MA}} = -(\Delta S_P / \Delta P_{MA})_{T_S} \tag{4d}$$

Any of the above relations, (4a)-(4d), could be used to quantify  $\Delta S_P$ , the human physiological entropy change.

Using the mechanical to human system mapping provided in the Table 1, let us consider the expression  $z = f(x,y)$  with  $z =$  physiological enthalpy (H);  $x =$  physiological entropy ( $S_p$ ); and  $y =$  mean arterial pressure ( $P_{MA}$ );  $M =$  skin temperature ( $T_s$ ); and  $N =$  heart rate ( $V_{HR}$ ). Using the enthalpy-based thermodynamic potential and invoking the exactness condition, we have, for the simple human physiological system shown on the right-hand side of Figure 1, the following absolute entropy change:

$$\Delta S_P = \left| (\Delta P_{MA} \times \Delta V_{HR}) / \Delta T_s \right| \quad (5)$$

Where,  $\Delta P_{MA} =$  Change in mean arterial pressure from relaxed to stressor and recovery states

$\Delta V_{HR} =$  Change in heart rate from relaxed to stressor and recovery states

$\Delta T_s =$  Change in skin temperature from relaxed to stressor and recovery states

$\Delta S_p =$  Change in physiological entropy change from relaxed to stressor and recovery states

The Equation (5) is based on the logic and examples demonstrated in Ref. [20]. If one were to consider either Internal energy or Gibbs function to define human physiological function, then one would get a negative sign preceding the entropy change ( $\Delta S_p$ ). This negative sign is ignored in this study because it is the magnitude of entropy departure that determines the change in the physiological state. This deviation may be positive or negative depending on the imposed external stressor and the internal physiological condition. As demonstrated in Aoki [13, 14], the physiological entropy change ( $\Delta S_p$ ) is given by  $\Delta S_p = S_{P_{flow}} + S_{P_{gen}}$ . Especially, physiological entropy generation,  $S_{P_{gen}}$ , is a kind of global measure which specifies how violent motions and reactions are occurring in nature. Hence, the entropy generation in the human physiological system shows the extent of activeness within the body as a whole; so the entropy generation is a significant quantity which characterizes the human body from thermodynamic and holistic (i.e., considering a human body as a whole) viewpoints. It has been demonstrated by Aoki [13, 14] that for human physiological system under basal or light exercise conditions, the  $S_{P_{gen}}$  is always positive that satisfies the second law of thermodynamics. On the other hand,  $S_{P_{flow}}$ , arising due to heat and mass transfer between the body and its environment, can be positive or negative. This would result in  $\Delta S_p$  acquiring either a positive or negative sign depending on the nature of activity and environmental conditions. Further, the net flow entropy being negative implies that human body absorbs “negative entropy” from its surroundings as Schrodinger [1] asserted. This is just the physical basis for ordered structures and functions in the human body to be maintained.

With this physical understanding, we consider only the absolute value of the entropy change for the purpose of this study. The human physiological entropy change could be considered as a composite measure of change in the whole physiological state in response to any external stimuli or stressor. However, if a single physiological indicator such as mean arterial pressure alone can provide that information, then why do we need this entropy change as a composite measure of physiological response? The answer is: The physiological concepts such as stimulus response (SR) specificity, organ response (OR) specificity, individual response specificity, and autonomic balance make the human physiological response a complex phenomena [21]. Furthermore, the human physiological system comprises of many interconnected physiological processes controlled by a complex nervous system. The single physiological indicators, in this regard, provide a very narrow representation of the human physiological stress response system. It is only by recognizing the interaction among human subsystems in their response to any stressor stimuli that one could build better model of human stress physiology. This study makes an effort to reduce the physiological complexity in terms of a composite entropy change.

### 3. METHODS

The data in the study was collected on eighty-two senior medical students and family medicine resident physicians (49 males and 33 females), who completed a standard physiological stress profile procedure routinely used for clinical assessment in the Primary Care Medicine Department at Eastern Virginia Medical School. The participants were all healthy (without any major health problems). The physiological data was collected by a ProComp+ biofeedback system connected to a Dell 166 MHz PC computer running a MultiTrace biofeedback software for data processing and analysis, as well as a stand-alone Dinamap 1846 Vital Signs Monitor (Critikon Inc., Tampa, FL). The Stress Profile (Stroops test) is a 20-minute standard testing sequence, during which mean arterial pressure, heart rate, and skin temperature from the palmar surface of the left hand little finger is collected continually during the three following conditions for each subject. The stress profile consists of following phases:

*State 1 (Relaxation Period): Relaxing in semi-reclining position with eyes open for three minutes followed by relaxing with eyes closed for three minutes (Total time = 6 minutes).*

*State 2 (Stressor Period): Solving a series of forty six-second long cognitive tasks presented on a computer screen – Stroops type color-naming tasks and arithmetic problems, which are alternated. The sequence of tasks is the same for all subjects (Total time = 8 minutes).*

*State 3 (Recovery Period): Relaxing again with eyes open for three minutes followed by relaxing with the eyes closed for three minutes (Total time = 6 minutes). With the Dinamap Vital Signs Monitor and using a mechanically inflated pressure cuff around the subject's right arm, the blood pressure and heart rate are recorded. Using the finger-cuff, the finger skin temperature was measured.*

The three physiological recordings were made after State 1 (relaxation period), State 2 (stressor period), and State 3 (recovery period), correspondingly. As one of the goals of the study was to examine the influence of stressors on physiology, the finger skin temperature was a better choice than the core body temperature.

#### 4. RESULTS AND ANALYSIS

The data analysis is performed to demonstrate the utility of Maxwell relations to measure physiological entropy change ( $\Delta S_P$ ) in terms of measurable mean arterial pressure (PMA), heart rate (VHR), and skin temperature (TS). Each one of these physiological measures used in the calculation of entropy change. For the purpose of illustration, let us consider the sample (n=49) of male subjects. The male average physiological measures during relaxation (State 1) are calculated as follows:

$$\begin{aligned}(P_{MA})_{\text{Relaxation}} &= 85.43 \text{ mm Hg} \\ (V_{HR})_{\text{Relaxation}} &= 58.49 \text{ bpm} \\ (T_S)_{\text{Relaxation}} &= 302.09 \text{ K}\end{aligned}$$

Let us consider the male average values during the Stressor Task (State 2). They are as follows:

$$\begin{aligned}(P_{MA})_{\text{Stress}} &= 90.08 \text{ mm Hg} \\ (V_{HR})_{\text{Stress}} &= 62.59 \text{ bpm} \\ (T_S)_{\text{Stress}} &= 300.72 \text{ K}\end{aligned}$$

The physiological entropy change at Stressor Task (State 2) is given by:

$$(\Delta S_P)_2 = \left| \frac{[(P_{MA})_{\text{Stress}} - (P_{MA})_{\text{Relaxation}}] \times [(V_{HR})_{\text{Stress}} - (V_{HR})_{\text{Relaxation}}]}{[(T_S)_{\text{Stress}} - (T_S)_{\text{Relaxation}}]} \right|$$

$$(\Delta S_P)_2 = \left| \frac{[(90.08-85.43) \times (62.59-58.49)]}{[300.72-302.09]} \right| = 13.92 \text{ mm Hg.bpm/K}$$

Let us consider the male average values during the Recovery (State 3). They are as follows:

$$\begin{aligned}(P_{MA})_{\text{Recovery}} &= 86.39 \text{ mm Hg} \\ (V_{HR})_{\text{Recovery}} &= 60.96 \text{ bpm} \\ (T_S)_{\text{Recovery}} &= 301.28 \text{ K}\end{aligned}$$

The physiological entropy change at Recovery (State 3) is given by:

$$(\Delta S_P)_3 = \left| \frac{[(P_{MA})_{\text{Recovery}} - (P_{MA})_{\text{Relaxation}}] \times [(V_{HR})_{\text{Recovery}} - (V_{HR})_{\text{Relaxation}}]}{[(T_S)_{\text{Recovery}} - (T_S)_{\text{Relaxation}}]} \right|$$

$$(\Delta S_P)_3 = \left| \frac{[(86.39-85.43) \times (60.96-58.49)]}{[301.28-302.09]} \right| = 4.23 \text{ mm Hg.bpm/K}$$

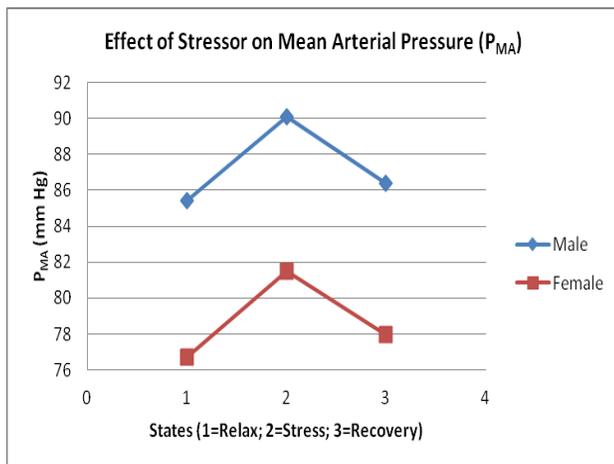
The physiological measures at states 1, 2, and 3 are summarized in Tables 2 and 3 and graphically demonstrated in Figures 2-5. The State 1 corresponds to relaxation and is used a reference state to compute change in entropy at state 2 (stressor) and state 3 (recovery), respectively. One can observe in Figures 2-4, the differences in individual physiological stress responses between male and female subjects. The mean arterial pressure and skin temperature responses are higher for males while the heart rate responses are lower in females. It is important to note that mean arterial pressure and heart rate increase from relaxation state to stressor while skin temperature decreases from relaxation to stressor state. There is an inverse relationship between hydrodynamic-related variables, mean arterial pressure and heart rate, and thermally-based skin temperature. It is noted that humans experience cold hands during a stressful situation. Further, once after the stressor is over and during the recovery state, the mean arterial pressure and heart rate decrease to a lower value, but to a value slightly higher than that of relaxed state. The skin temperature on the other hand, increases but to a value lower than that of relaxed state. The individual physiological responses provide limited information about the physiological impact of stressors. However, when they are combined in the form of a physiological entropy change, one can look at the integrated physiological stress response as demonstrated in Figure 5. The relaxation state is taken as the reference, and the entropy change from this reference state to stressor and recovery states are computed. It is clear from Figure 5 that physiological entropy change in female subjects is greater than that of males at both states 2 and 3.

**Table 2: Average Male Physiological Stress Responses**

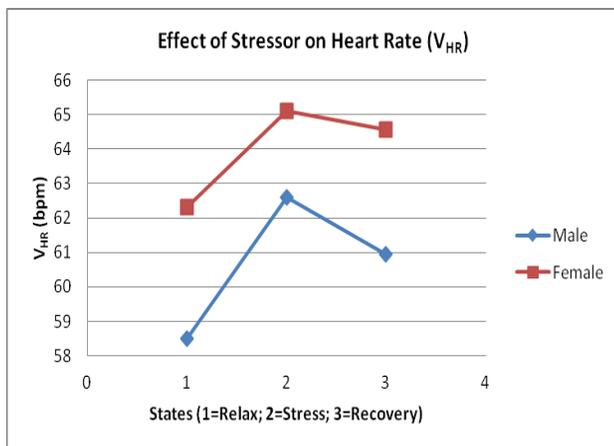
Physiological Measures	State 1 (Relaxation)	State 2 (Stress)	State 3 (Recovery)
$P_{MA}$ , mm Hg	85.43	90.08	86.39
$V_{HR}$ , bpm	58.49	62.59	60.96
$T_S$ , K	302.09	300.72	301.28
$\Delta S_P$ , mm Hg.bpm/ K	-	13.92	4.23

**Table 3: Average Female Physiological Stress Responses**

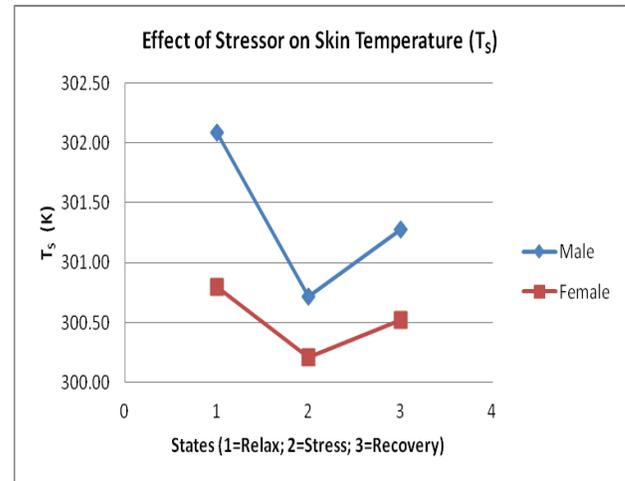
Physiological Measures	State 1 (Relaxation)	State 2 (Stress)	State 3 (Recovery)
$P_{MA}$ , mm Hg	76.73	81.48	77.97
$V_{HR}$ , bpm	62.30	65.09	64.55
$T_s$ , K	300.80	300.31	300.52
$\Delta S_p$ , mm Hg.bpm/ K	-	27.05	9.03



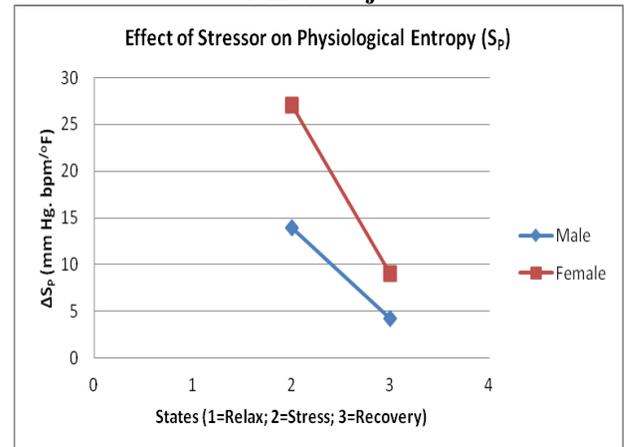
**Figure 2. Changes in average mean arterial pressure for male and female Subjects**



**Figure 3. Average changes in heart rate for male and female subjects**



**Figure 4. Changes in skin temperature for male and female subjects**



**Figure 5. Changes in physiological entropy for male and female subjects**

## 5. CONCLUSION

An analytical model to quantify entropy change in human physiology is developed. The study is based on the premise that Maxwell relations could be used to compute entropy change in terms of measurable physical variables. The pressure, volume, and temperature are equated to mean arterial pressure, heart rate, and skin temperature. Using this analogy, physiological entropy change is computed in both male and female subjects. The experimental study involved 49 male and 33 female subjects and it was conducted in a medical school. The physiological variables were measured at three states, relaxed, stressor task, and recovery. The physiological measures taken during relaxation were taken as the reference. The physiological changes in mean arterial pressure, heart rate, and skin temperature from the reference (state 1) to stressor (state 2) and recovery (state 3) were combined using Maxwell relations to compute entropy changes. The results indicate difference in individual physiological stress responses

between male and female subjects. When these physiological responses are combined in the form of an entropy change, it provides a systems view of human physiological stress response. This integrated physiological entropy change might be of value to medical researchers who are interested in examining whole human physiological stress responses. It is, however, beyond the scope of this study to make any physiological or medical interpretation of entropy change in human systems. The main purpose of this study was to demonstrate the utility of Maxwell relations in human physiology.

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