Modeling of the Renin Angiotensin Aldosterone System during Pregnancy

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***ABSTRACT** - The renin-angiotensin-aldosterone system (RAAS) is critical in facilitating the proper balance of blood pressure. When lower blood pressure is detected, a cascade of hormonal secretion and enzymatic activity takes the inactive form of renin and converts it to angiotensin and aldosterone to perform vasoconstriction and kidney salt-retention, respectively. In this paper, we attempt to model the RAAS system by specifically examining the conversion of renin to angiotensin II in the context of pregnancy. Its mathematical equations were utilized to build a Simulink model, and further characterization was done via Laplace Transform and Bode analysis. This study attempts to shed light on the implications of pregnancy on blood pressure control in humans.*

***KEYWORDS** - systems biology, renin, angiotensin, blood pressure, pregnancy, Simulink.*

I. INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is an important regulator of blood pressure and blood electrolyte level. It relies upon a feedback system that begins with the secretion of renin and ends with the release of angiotensin II and aldosterone and an increase in blood pressure. This hormone cascade is activated during hypotension. Low blood pressure leads the juxtaglomerular cells in the kidneys to convert prorenin to renin. Renin would then catalyze the conversion of angiotensinogen (formulated in the liver) to angiotensin I, and the angiotensin-converting enzyme (ACE) in lungs and kidneys would then be able to convert this physiological inactive precursor to angiotensin II. Angiotensin II primarily functions as a vasoconstrictor by acting on AT1 and AT2 receptors throughout the body, thereby increasing blood pressure. It also acts on the adrenal cortex in the kidney, stimulating the release of aldosterone. Aldosterone promotes the reuptake of sodium back into the blood and the excretion of potassium in the kidney nephrons, driving more fluid back into the blood, and thereby further increasing blood pressure [1][2].

Though the role of RAAS in the human body has been well established, its critical function in women undergoing pregnancy, and its potential lethal causes of chronic hypertension, superimposed preeclampsia, and eclampsia is less understood. Specifically, RAAS is different in pregnancy as it involves the increase in stress to the maternal cardiovascular system and the potentially dangerous influence of the renin "leak" from the placenta. In this project, we attempt to develop a basic mathematical model using Simulink that would provide an overview of how the RAAS system would act to increase the blood pressure of women undergoing pregnancy. The scope of this modeling would be limited to the process where renin converts to angiotensin I and angiotensin II, and the changes in the amount of angiotensin II bound to AT1 receptors will be monitored. Changes in plasma renin activity (PRA), angiotensinogen (AGT), angiotensin I (AngI), angiotensin II (AngII), and bound AngII to AT1 receptor concentrations as a result of pregnancy will be visualized as the outputs of this model. Analysis of this system using Laplace transform and Bode Plots will also be conducted. The goal would be to compare the outputs between pregnant women and non-pregnant women to better understand the cause of important diseases related to pregnancy such as preeclampsia.

II. MATHEMATICAL MODEL

The equations that will be used for this model were derived from the text published by the American Association for Pharmaceutical Scientists in 2011:

$$[PRA] = \frac{V_{max}[AGT]}{[AGT]+[AGT]_0} * f([AT1-AngII_{bound}])$$

(1)

$$\frac{d[AGT]}{dt} = k_{AGT} - [PRA] - \frac{ln(2)}{h_{AGT}}[AGT]$$

(2)

$$\frac{d[AngI]}{dt} = [PRA] - K_1[AngI]$$

(3)

$$\frac{d[AngII]}{dt} = K_2[AngI] - K_3[AngII] \tag{4}$$

$$\frac{d[AT1-AngII_{bound}]}{dt} = c_{AT1}[AngII] - \frac{ln(2)}{h_{AT1}}[AT1 - AngII_{bound}] \tag{5}$$

where,

$$K_1 = c_{ACE} + c_{CHY} + c_{NEP} + \frac{ln(2)}{h_{AngI}}$$

$$K_2 = c_{ACE} + c_{CHY}$$

$$K_3 = c_{ACE2} - c_{AngII->AngIV} - c_{AT1} - c_{AT2} + \frac{ln(2)}{h_{AngII}}.$$

The variables represent various constants and concentration values of the RAS system:

- V_max: maximum rate of reaction 4 as dictated by the Michaelis-Menten model (1/hr).
- [AGT]/[AngI]_0: initial blood angiotensinogen/angiotensin I levels prior to pregnancy (ng/mL).
- [AT1-AngII_bound]: remaining concentration of free AT1 receptors available for binding (ng/mL).
- [PRA]: concentration of plasma renin activity (ng/mL/hr).
- h_AGT/AngI/AngII/AT1: half-life of angiotensinogen/ angiotensin I/ angiotensin II/ AT1 receptor (hr).
- c_ACE/ACE2: first-order rate constant of the enzymatic kinetics of ACE/ACE2 conversion of AngI to AngII (1/hr).
- c_CHY: first order rate constant of the enzymatic kinetics of chymase conversion of AngI to AngII (1/hr).
- c_NEP: first order rate constant of the neutral endopeptidase hydrolysis of AngI and AngII to generate Ang-(1-7) (1/hr).
- c_AngII->AngIV: first order rate constant of the conversion of AngII to AngIV (1/hr).
- c_AT1/AT2: binding rate to AT1/AT2 receptors (1/hr).
- k_AGT: angiotensinogen synthesis rate (ng/mL/hr).

The values of these variables were derived from literature, and most of them are assumed to be the same between pregnant and non-pregnant women except for initial AGT levels, initial angiotensin I levels, and [AT1-AngII_bound]. The values can be found in Table 1.

TABLE 1				
Variable	Pregnant	Not Pregnant	Units	Source
[AGT]_0	3100	1000	ng/mL	[4]
[AT1-AngII_bound]*	0.10	0.033	ng/mL	[3]
[PRA] or V_max	2.4	0.34	ng/mL/hr	[3][4]
h_AGT	16	16	hr	[3]
c_ACE	54.1	54.1	1/hr	[3]
c_CHY	1.1	1.1	1/hr	[3]
c_NEP	1.1	1.1	1/hr	[3]
h_AngI	0.0083	0.0083	hr	[3]
[AngI]_0**	0.0465	0.015	ng/mL	[3]
c_ACE2	2.4	2.4	1/hr	[3]
c_AngII->AngIV	23.5	23.5	1/hr	[3]
c_AT1	1.15	1.15	1/hr	[5]
c_AT2	1.15	1.15	1/hr	[5]
h_AngII	0.0083	0.0083	hr	[3]
h_AT1	0.2	0.2	hr	[3]
k_AGT	0.00002	0.00002	ng/mL/hr	[3]

TABLE 1. Shows the values of each variable in the five equations for this model. * represents that those values are calculated as 0.0033% of [AGT]_0. ** represents that those values are calculated as 0.0015% of [AGT]_0.

Taking these values into account, the three constants will equal:

$$K_{1,non-pregnant} = K_{1,pregnant} = 139.81 \ hr^{-1}$$

$$K_{2,non-pregnant} = K_{2,pregnant} = 55.2 \ hr^{-1}$$

$$K_{3,non-pregnant} = K_{3,pregnant} = 60.11 \ hr^{-1}$$

Leaving [AGT]_0, [AT1-AngII_bound], and [AngI]_0 values as values that will be different between pregnant and non-pregnant
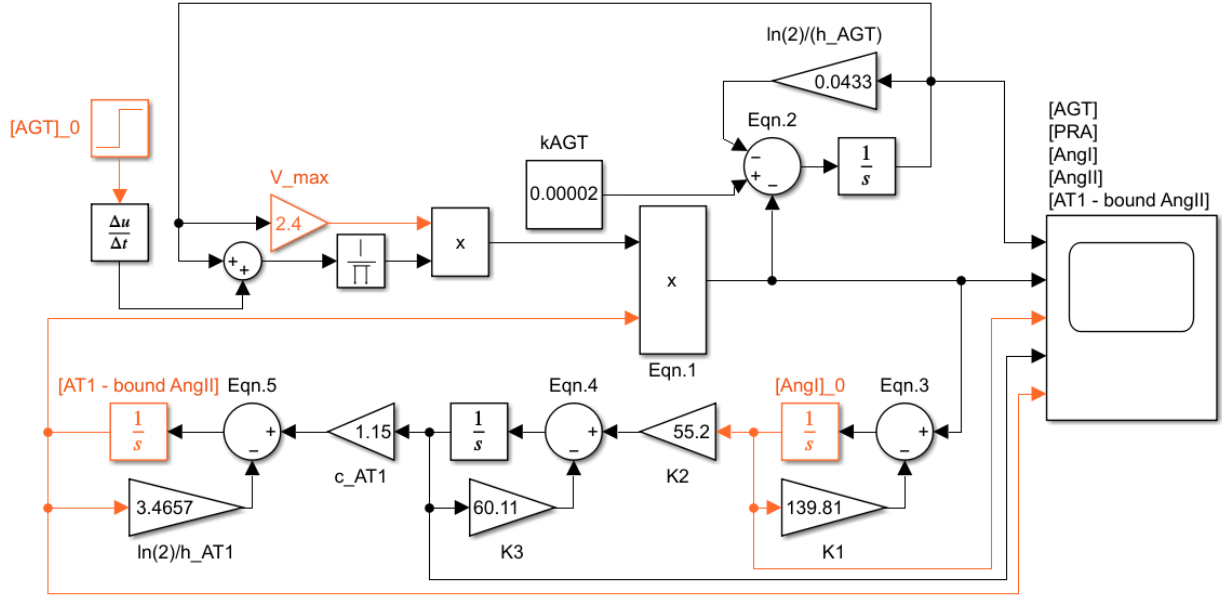
Figure 1. The renin-angiotensin system model for pregnancy derived using Simulink. Blocks and paths with orange tracing represents those that have different initial conditions between non-pregnant and pregnant women, while the others have the same initial conditions regardless.

women. These values were determined with various assumptions and simplifications.

III. ASSUMPTIONS

In order for the numbers to be derived and for the model to be simple enough, several assumptions have been made. In terms of the value derivation, these include:

1. The values of [AT1 - AngII_bound] can be modeled as a percentage of [AGT]_0. The values of [AT1 - AngII_bound] can be found in Table 20.3 from Ref. [3], but however, it was modeled for a hypothetical patient with an extremely low [AGT]. In order for the model to make sense, the percentage of [AT1 - AngII_bound] to [AGT] in Table 20.3 were taken and applied to the value of [AGT]_0 in Table 1 to derive the value for [AT1 - AngII_bound].

2. The values of [AngI]_0 can be modeled as a percentage of [AGT]_0. Same logic here as assumption 1, but with a different value to normalize.

    3. The values that are identical between non-pregnant and pregnant women accurately reflect, or at least

approximate, the physiological status of both types of patients.

4. The values in Table 20.2 and 20.3 from Ref. [3] can be utilized to represent the endocrinology of women undergoing or not undergoing pregnancy.

5. The values for pregnant women represent the values that were collected after 20 weeks into pregnancy, which is when most cases of preeclampsia and other worse conditions are first diagnosed.

6. The feedback function in Eqn.1 can be approximated purely by [AT1 - AngII_bound].

And for the model to work, several other assumptions also need to be made [3]:

1. Modeling the system as an impulse of different initial conditions between pregnant and non-pregnant women for [AGT]_0, V_max, [AT1 - bound AngII], and [AngI]_0 can represent the physiological outcomes of these hormones.

2. The rate of substrate conversion between PRA and AngI can be modeled with the Michaelis-Menten

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model where V_max would be the rate of synthesis of PRA ([PRA]).

3. The instantaneous amount of AngII bound to AT1 has a negligible effect on the blood concentration of AngII.
4. AngII binds almost exclusively to AT1 receptors.
5. Steady-state equilibrium can be used to determine the calculation of various variable values.

And thus, with these assumptions, a Simulink model can be made to model the RAAS.

IV. SIMULINK MODEL

The model was developed in Simulink and represented in Figure 1. The model is predicated on the assumption that the values obtained in Table 1, which are derived from patient samples from various studies, represent an instantaneous increase of such concentration from baseline, and that the system response thereafter represents the physiological system's response without additional input. Through modeling the system's response to one impulse from either pregnant patients or non-pregnant patients, the values of bound AngII to AT1 receptors can be monitored.
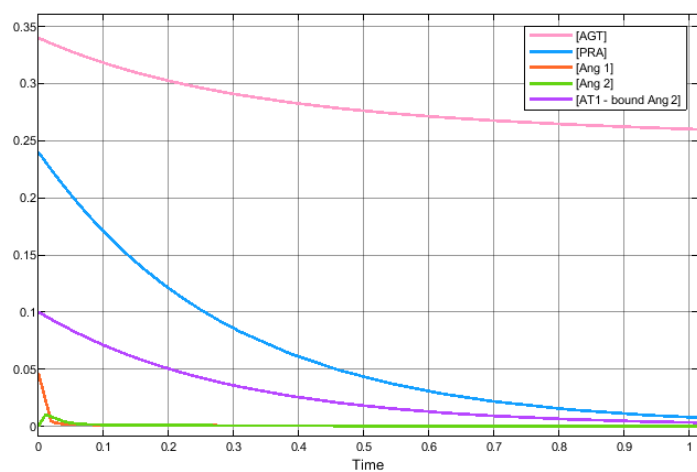

Figure 2a. The Simulink output for pregnant patients. Units of [x] and [y] axis are [hr] and [ng/mL].
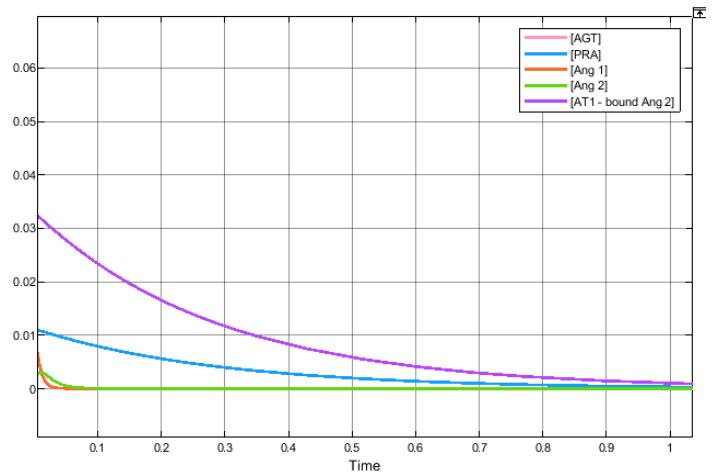

Figure 2b. The Simulink output for non-pregnant patients. [AGT] was cropped from this graph but represents similar values as Figure 2a. Units of [x] and [y] axis are [hr] and [ng/mL].

As represented in Figure 2a and Figure 2b, the rate of drop to an arbitrary value of [AT1 - bound AngII] (e.g. 0.01 ng/mL) for non-pregnant patients is in about 0.34hr, while for pregnant patients, the concentration drops in twice the time, 0.68hr. This can be explained by the starting impulse for pregnant patients being higher than non-pregnant patients, causing the bound AngII levels to remain at a much higher concentration for pregnant patients than non-pregnant patients over the same time interval. Furthermore, the higher the concentrations of bound AngII and AngII in the system, the greater the degree of vasoconstriction and aldosterone release, leading to higher salt retention in the kidney medulla. These two physiological change results directly in the increase of blood pressure, and if the system is to be modeled across countless impulses at intervals unknown in the field, then the blood pressure will be maintained at a level dictated by the concentration of bound AngII. Thus, the higher retention of bound AngII in pregnant patients, even just by two-fold, over the same time interval will lead to chronic hypertension, a precursor to serious illnesses like preeclampsia.

An additional trend to note is that for both the pregnant and non-pregnant patients, the values of [PRA], [Ang1], [Ang2], and [AT1-bound Ang2] all trend towards zero as time goes on. This trend makes sense physiologically because it shows that the body is creating a negative feedback loop in response to the impulse that is input into [PRA]. This fits with the purpose of the RAAS which is to regulate blood pressure. If any of these

hormones became elevated for too long this could lead to serious deleterious effects on the body as blood pressure could increase beyond healthy physiological normal values.

V. LINEARIZATION AND LAPLACE TRANSFORM

The model can be further analyzed by taking the Laplace transform for the linearized version of Equations 1~5:

$$[PRA] = \frac{V_{max}*[AGT]_{ss}}{[AGT]_{ss}+[AGT]_0}\overline{[AT1-AngII_{bound}]} + \overline{[AT1-AngII_{bound}}$$

$$\overline{\frac{}{[AGT]}} * \frac{((1-V_{max})[AGT]_{ss}+[AGT]_0)(V_{max}(k_{AGT}-[PRA]_{ss}-\frac{ln(2)*[AGT]_{ss}}{h_{AGT}}}{([AGT]_{ss}+[AGT]_0)^2}$$

$$= C * \overline{[AT1-AngII_{bound}]} + D * \overline{[AGT]}$$

$$C = -.002, D = -2.3*10^{-8},$$
$$[AGT]ss = (.00002 - .34)*16/ln(2) = -7.8$$

(6)

$$\frac{d\overline{[AGT]}}{dt} = -\overline{[PRA]} - \frac{ln(2)}{h_{AGT}}\overline{[AGT]}$$

(7)

$$\frac{d\overline{[AngI]}}{dt} = \overline{[PRA]} - K_1\overline{[AngI]} \qquad (8)$$

$$\frac{d\overline{[AngII]}}{dt} = K_2\overline{[AngI]} - K_3\overline{[AngII]} \qquad (9)$$

$$\frac{d\overline{[AT1-AngII_{bound}]}}{dt} = c_{AT1}\overline{[AngII]} - \frac{ln(2)}{h_{AT1}}\overline{[AT1-AngII_{bound}]}$$

(10)

Values of C and D were found by assuming steady-state values approach values from Table 1. [AGT]ss was found by assuming equation 2 equals 0. The following laplace transforms were taken on the linearizations of equations [6-10]:

$$[PRA](s) = C * [AT1-AngII_{bound}](s) + D * [AGT]$$

(11)

$$s[AGT](s) = \frac{k_{AGT}}{s} - [PRA](s) - \frac{ln(2)}{h_{AGT}}[AGT](s) + [AGT]_0$$

(12)

$$s[AngI](s) = [PRA](s) - K_1[AngI](s) + [AngI]_0$$

(13)

$$s[AngII](s) = K_2[AngI](s) - K_3[AngII](s) + [AngII]_0$$

(14)

$$s[AT1-AngII_{bound}](s) = c_{AT1}[AngII](s) \ldots$$
$$- \frac{ln(2)}{h_{AT1}}[AT1-AngII_{bound}](s) + [AT1-AngII_{bound}]_0$$

(15)

The next logical step is to calculate a closed loop transfer function using [AT1-AngII$_{bound}$] as our input, and [PRA] as our input. This would give us an idea of how the dynamics of [PRA] would affect the dynamics of the final physiologically relevant product which would have an effect on the body. A transfer function analysis aids in understanding the stability of the system, and looking at the poles and zeros. Below are some of the preliminary calculation steps:

$$[AngI](s) = \frac{[PRA](s)+[AngI]_0}{s+K_1}$$

(16)

$$[AngII](s) = \frac{K_2([PRA](s)+[AngI]_0)+[AngI]_0(s+K_1)}{s+K_1(s+K_3)}$$

(17)

$$[AT1-AngII_{bound}](s) =$$
$$\frac{c_{AT1}(K_2([PRA](s)+[AngI]_0)+[AngI]_0(s+K_1))+[AT1-AngII_{bound}]_0(s+K_1)(s+K_3)}{s+K_1(s+K_3)(s+\frac{ln(2)}{h_{AT1}})}$$

(18)

In further research, we would aim to apply some simplifications to this system of equations and complete the laplace analysis, including a bode plot of the system. Although we did not complete such an analysis here, there are some key points to note. Importantly, the poles of the sub-transfer functions are equal to K_1, K_3, and $ln(2)/h_{AT1}$. This means that these quantities most affect the dynamics of the relationship between the two variables that we are looking at.

VI. CONCLUSIONS

The field of women's health is notoriously understudied, and we were not able to find robust, peer reviewed research on the effects of pregnancy on renin. Renin is the first biomolecule in the RAAS cascade, and high concentrations can lead to overproduction of the pathway products, and have adverse health effects on the patient's cardiovascular system. In general, the physiological changes in the body during pregnancy are still being researched, and the long term effects of pregnancy on human organs are not clear.

Our work has the potential to help us build a digital model of the state of pregnancy with respect to the RAAS, which could help researchers run simulated experiments to determine the effects of drugs on blood pressure, preeclampsia, and hypertension. The model successfully demonstrated the longer settling time the pregnant model of the system exhibits after a perturbation, or activation of plasma renin activity. However, modeling the frequency of activation and effects of high baseline renin levels is a challenge yet to be met. Our work aims to spark further conversation on how to improve this model, and highlight the importance of studying the human system under different important physiological conditions.

Pregnancy is quite literally vital to the survival of the human race, yet there is very little computational research or efforts to model how the body is different while pregnant. Although our work presents an imperfect simulation, a computer model such as this one could also prove useful for running quick and risk-free experiments to understand the effects of drugs or medical treatments on pregnant patients.

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