Modeling of the Renin Angiotensin Aldosterone System during Pregnancy

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Professor Cauwenberghs

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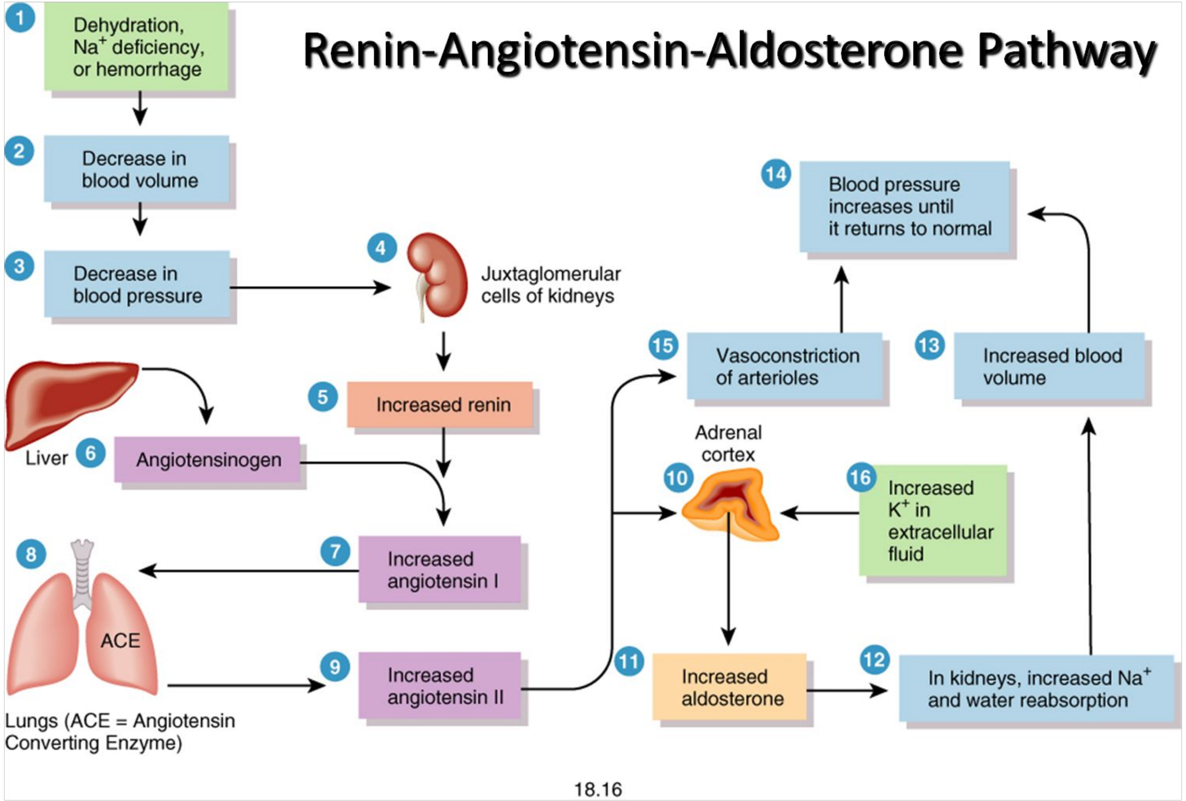
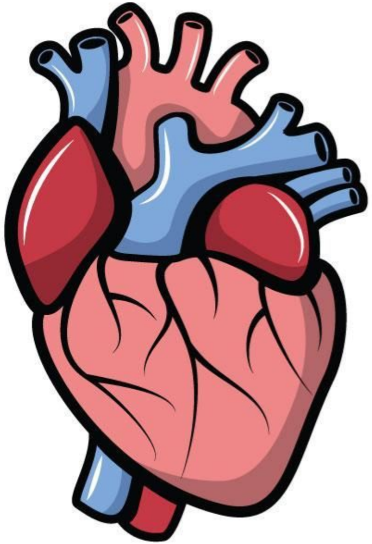
Intro / Physiology



Intro / Physiology



Equations

$$[PRA] = \frac{V_{max}[AGT]}{[AGT]+[AGT]_0} * f([AT1 - AngII_{bound}]) \quad (1)$$

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

$$\frac{d[AngI]}{dt} = [PRA] - K_1[AngI] \quad (3)$$

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

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

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

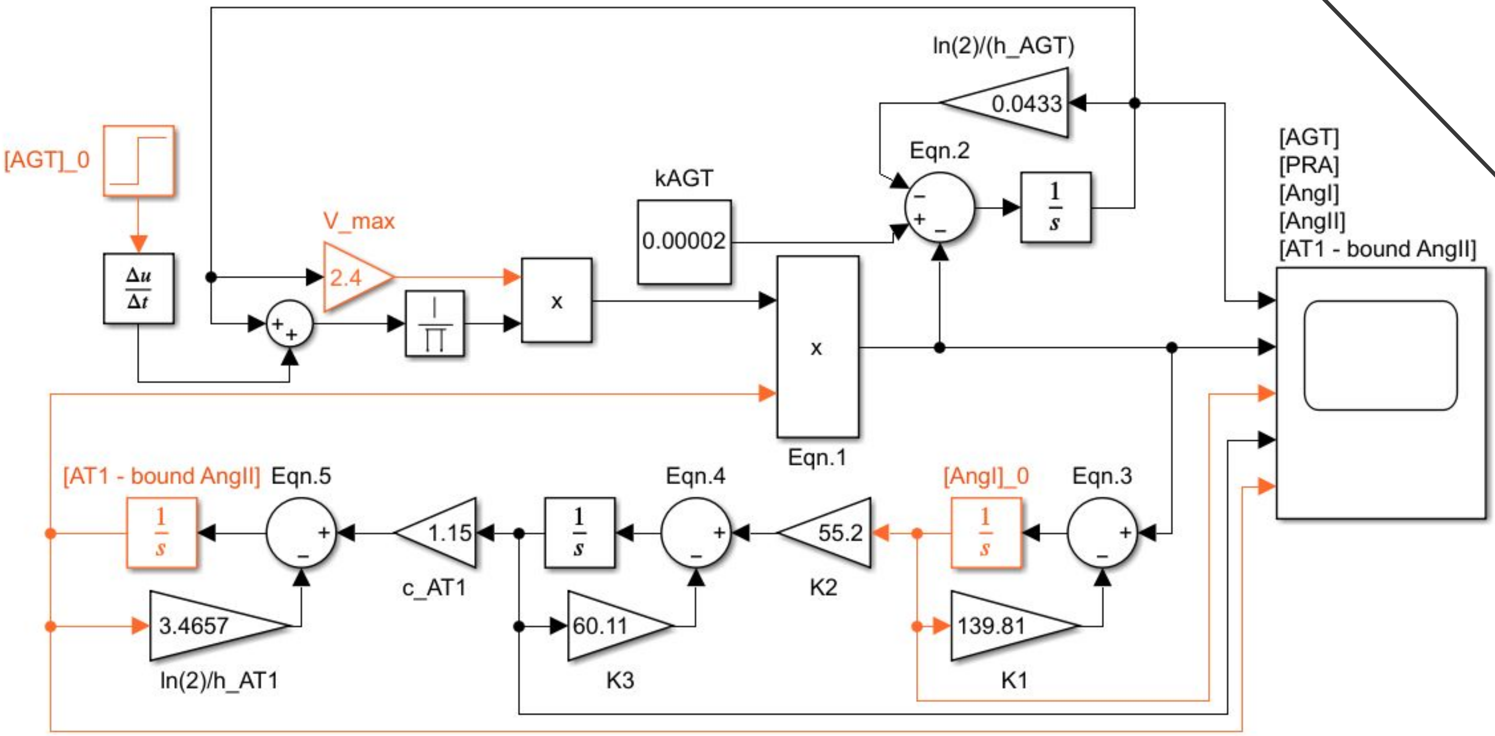
$$K_2 = c_{ACE} + c_{CHY}$$

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

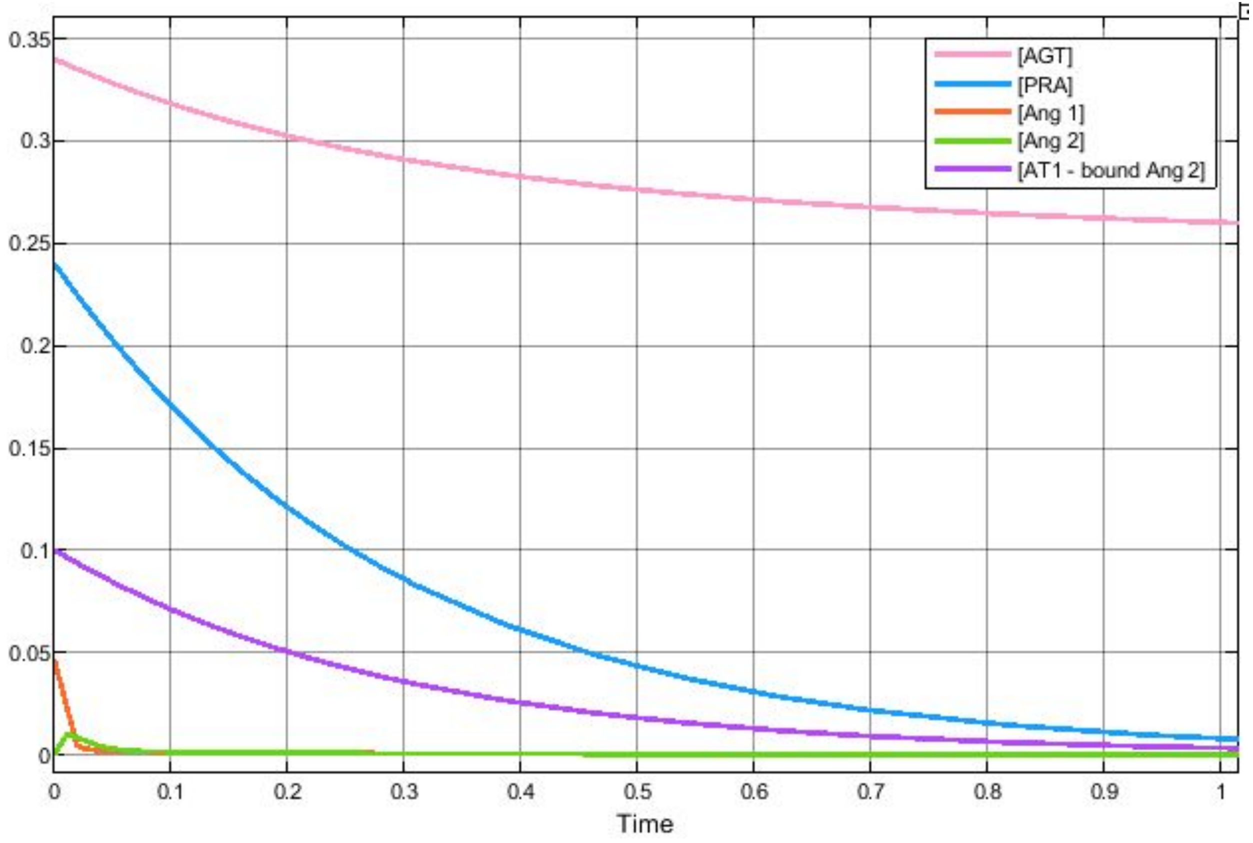
VALUES

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]	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]

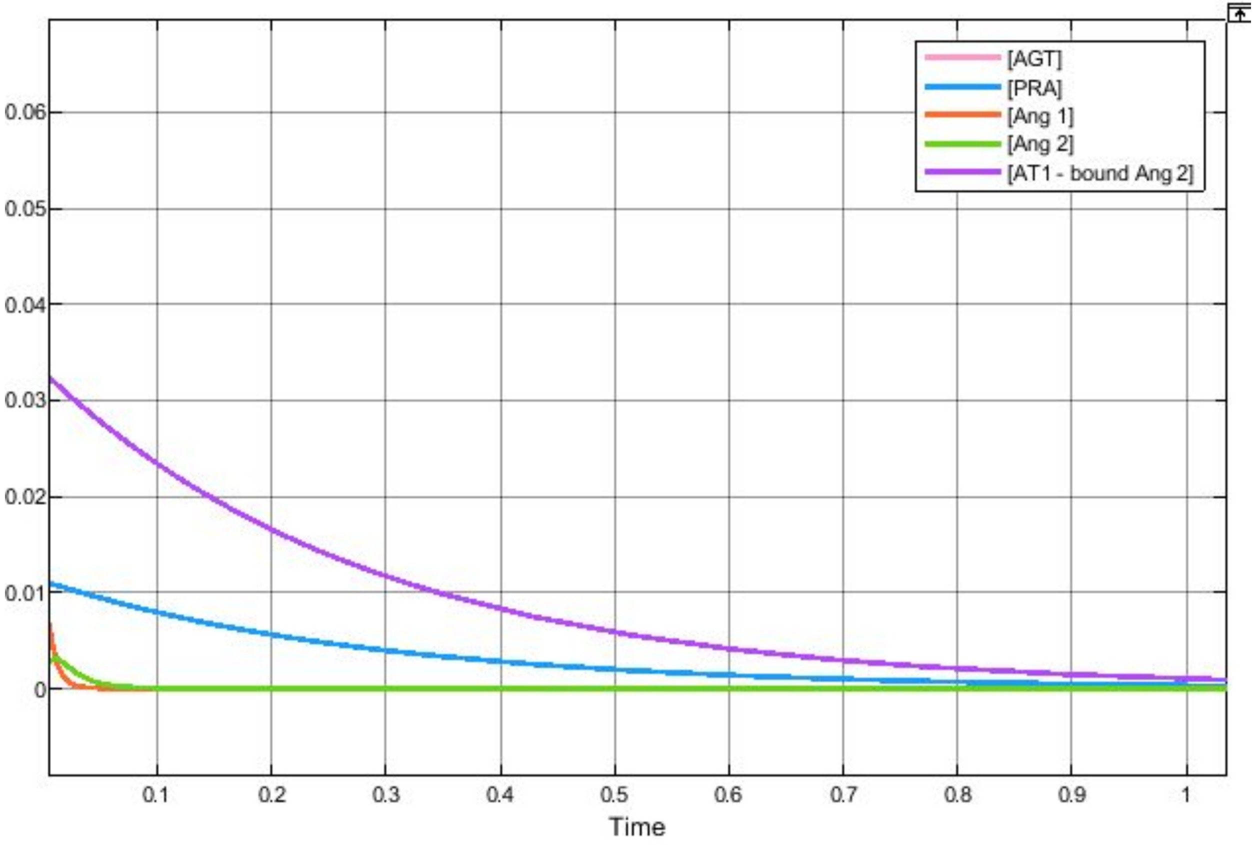
Simulink Model



SIMULINK OUTPUT



SIMULINK OUTPUT



LINEARIZATION

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

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

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

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

$$[PRA] = \frac{([AGT]ss+[AGT]_0) * \frac{d}{dt}[V * [AGT]ss] - V * [AGT]ss * \frac{d}{dt}[[AGT]ss+[AGT]_0]}{([AGT]ss + [AGT]_0)^2}$$

$$* ([\sim AT1 - \sim AngII]) + \frac{V * [\sim AGT]}{[\sim AGT] + [AGT]0} * \frac{d}{dt}[AT1ss - AngIIboundss]$$

Laplace Analysis

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

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

$$s[\widetilde{AngII}](s) = K_2[\widetilde{AngI}](s) - K_3[\widetilde{AngII}](s) \ + [\widetilde{AngII}]_0$$

$$s[\widetilde{AT}1 - \widetilde{AngII_{bound}}](s) = c_{AT1}[\widetilde{AngII}](s) - \frac{\ln(2)}{h_{AT1}}[\widetilde{AT}1 - \widetilde{AngII_{bound}}](s) + [\widetilde{AT}1 - \widetilde{AngII_{bound}}]_0$$

Conclusions & Applications

- Physiological changes during pregnancy are poorly understood.
- Cardiovascular Side Effects
- Drug kinetics
- Safety of computer model

Next Steps

- Model consistent activation of the RAAS as a square wave of impulses
- Complete Laplace Analysis
- Perform bode analysis in MATLAB

THANK YOU!

Questions?