Project: “The Cardiovascular System & Norepinephrine”
CSC-432
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The major player in the cardiovascular system is the heart. The heart is regulated by the autonomic nervous system. The autonomic nervous system is broken down into 2 divisions: the sympathetic and the parasympathetic nervous systems. The sympathetic nervous system stimulates heart rate while the parasympathetic nervous system inhibits heart rate via the vagus nerves. The effects of both of these systems on heart rate can be represented by the following equation:

$HR_{sv} = HR_v + (HR_s – HR_0) (HR_v – HR_{min})/(HR_0 – HR_{min})$,

where:

HR_{sv} = heart rate value due to vagus stimulation and sympathetic stimulation
HR_v = heart rate value due to vagus stimulation
HR_s = heart rate value due to sympathetic stimulation
HR_0 = heart rate value due to no stimulation
HR_{min} = minimum heart rate achievable by vagus stimulation alone short of complete arrest.

As one can see from this equation, heart rate is linearly dependent on both the sympathetic and parasympathetic nervous system. Also, the parasympathetic nervous system is capable of dominating the sympathetic nervous system in controlling the heart. (“Effect of Combined Sympathetic and Vagal Stimulation on Heart Rate in the Dog” Homer R. Warner, M.D., Ph.D., and Richard O. Russell, Jr., M.D.)

Delving into the parasympathetic nervous system further, one will discover that vagus nerve fibers have vesicles at their endings that contain acetylcholine. When signaled, these vesicles discharge acetylcholine into the S-A node. Based on the concentration of acetylcholine in the S-A node, heart rate will be decreased accordingly. In “Effect of Combined Sympathetic and Vagal Stimulation on Heart Rate in the Dog” by Homer R. Warner, M.D., Ph.D., and Richard O. Russell, Jr., M.D., the following equations were derived to illustrate this effect:

$HR_v = 60/P_v$
$P_v = P_o + K_{10}C_2$ for $C_2 < a$
P_v = infinity for $C_2 > a$
$dC_2/dt = (nK_8NC_1f_2-K_9C_2)/V_2$
$dN/dt = K_7(N_m-N)- K_8Nf_2$

where:

P_v = the period of the heart cycle due to vagal stimulation
P_o = the period of the heart cycle without any stimulation
K_{10} = proportional constant
C_2 = acetylcholine concentration at the S-A node
a = critical C_2 value constant (if crossed will stop the vagus nerve entirely)
n = number of fibers stimulated
K_8 = fraction of vesicles discharged per action potential per stimulus per fiber
N = average number of vesicles at each nerve ending charged with acetlycholine
C_1 = acetylcholine concentration in vesicles (assumed to be a constant here)
f_2 = frequency of supramaximal stimulation of the vagus nerve

K_9 = proportional constant
V_2 = volume into which acetylcholine is diluted at the S-A node
K_7 = proportional constant
N_m = the maximum number of vesicles when no stimulus has been present for some time.

Based on the equations above and holding the sympathetic nervous system constant, a model of the regulation of heart rate by the autonomic nervous system can be seen in the following figure:

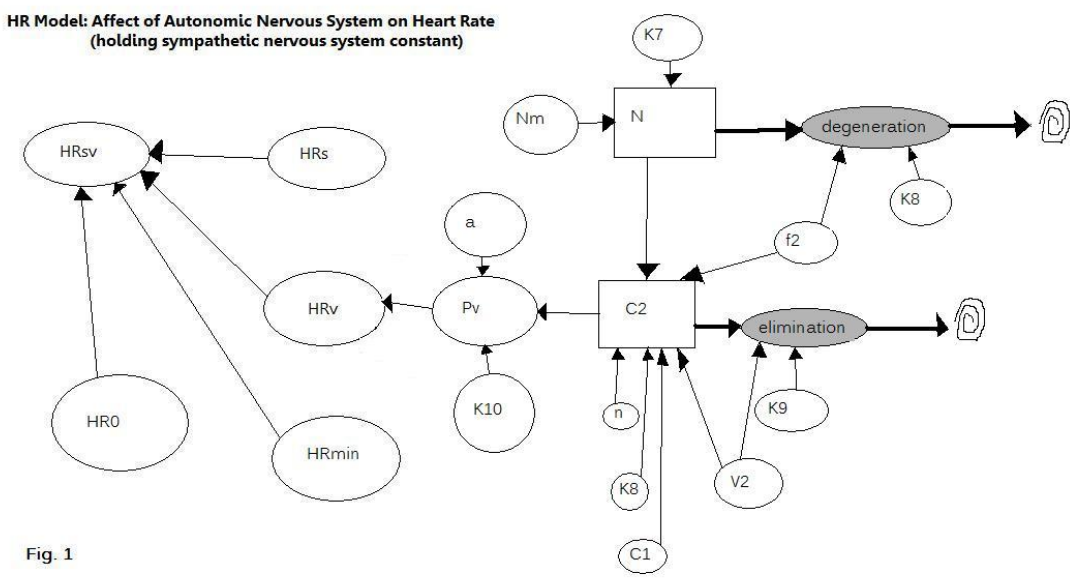
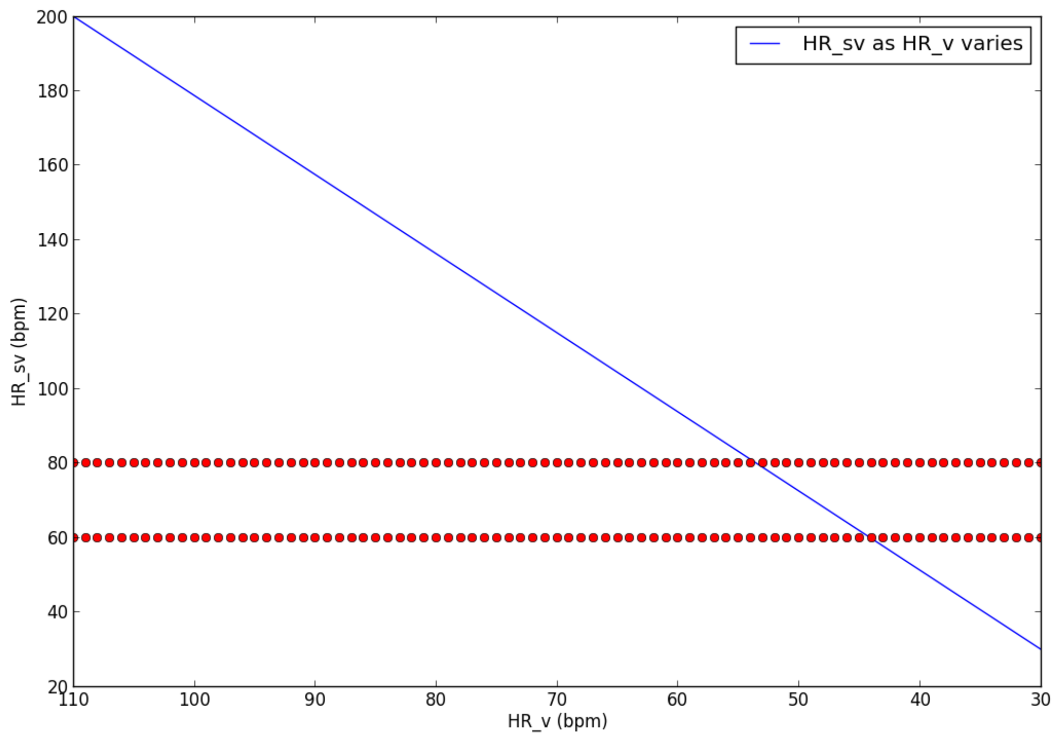


Fig. 1

Using the model in Fig. 1 and the equations above, a simulation can be run to determine heart rate, HR_{sv}. As stated in Shiflet and Shiflet, the intrinsic rate of the heart is 100-115bpm (HR_0). Let's assume HR_0 = 110bpm. Also, let's assume HR_s is constant and equals a high 200bpm. Finally, as stated in Warner & Russell, HR_{min} is known to equal 30bpm. A distribution (*generated by final_project_pinckney.py*) of HR_{sv} as HR_v varies can be seen below:



When a normal adult is at rest, their heart rate is usually 60-80bpm. This normal range is indicated in the graph above by the red dots. As one can see, the heart rate due to vagus stimulation (HR_v) would need to be 53-44bpm if the person in this simulation is to have a resting heart rate (HR_{sv}) of 60-80bpm.

This heart rate model can be taken a step futher by incorporating an element of the sympathetic nervous system: epinephrine (adrenalin) / norepinephrine (noradrenaline). The following equations, derived in “Dynamics of heart rate response to sympathetic nerve stimulation” by Abdelkader Mokrane and Réginald Nadeau, describe the effect of norepinephrine on heart rate:

$$\Delta\mathrm{HR} = G([\mathrm{NE}]) = \frac{\Delta\mathrm{HR}_{\max}[\mathrm{NE}]^2}{K_{\mathrm{NE}}^2 + [\mathrm{NE}]^2}$$

and

$$K_{\mathrm{NE}} = K_f \tau_{\mathrm{NE}}$$

where:

G = the steady-state HR response
[NE] = step increase of norepinephrine concentration

ΔHR_{max} = the maximum value of ΔHR (= 72.6bpm)
K_{NE} = the [NE] producing a half-maximum response
K_f is the stimulation frequency producing a half-maximum response (= 1.21Hz)
τ_{NE} = the time constant of the NE removal process (= 9.1s on average).

As a result, the heart rate model can be updated to look like the following:

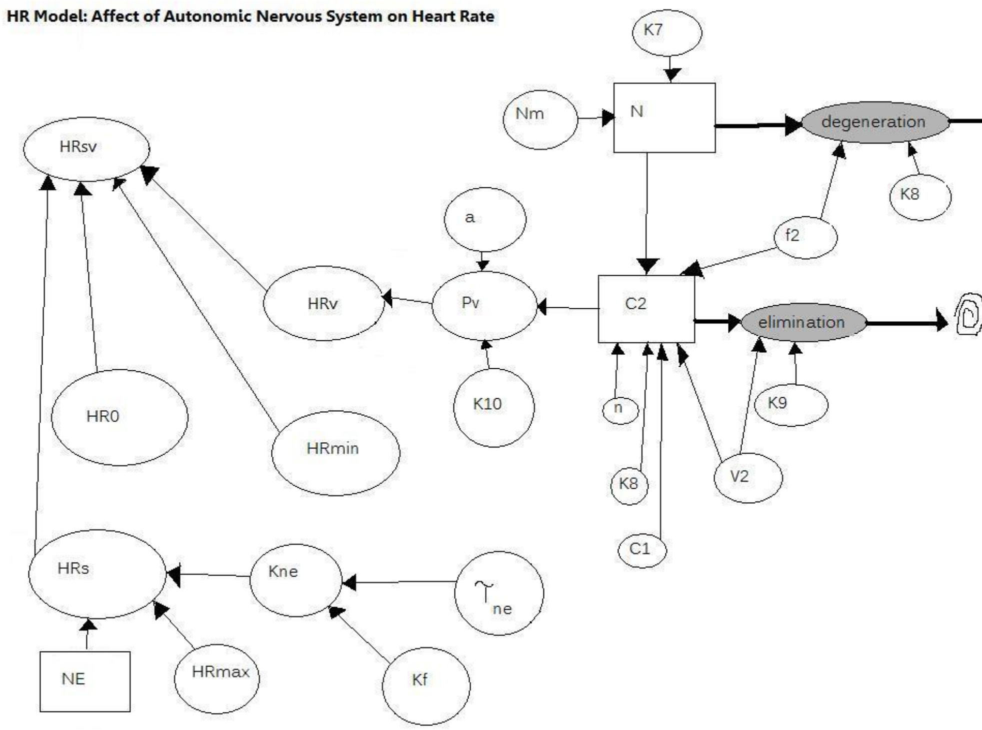
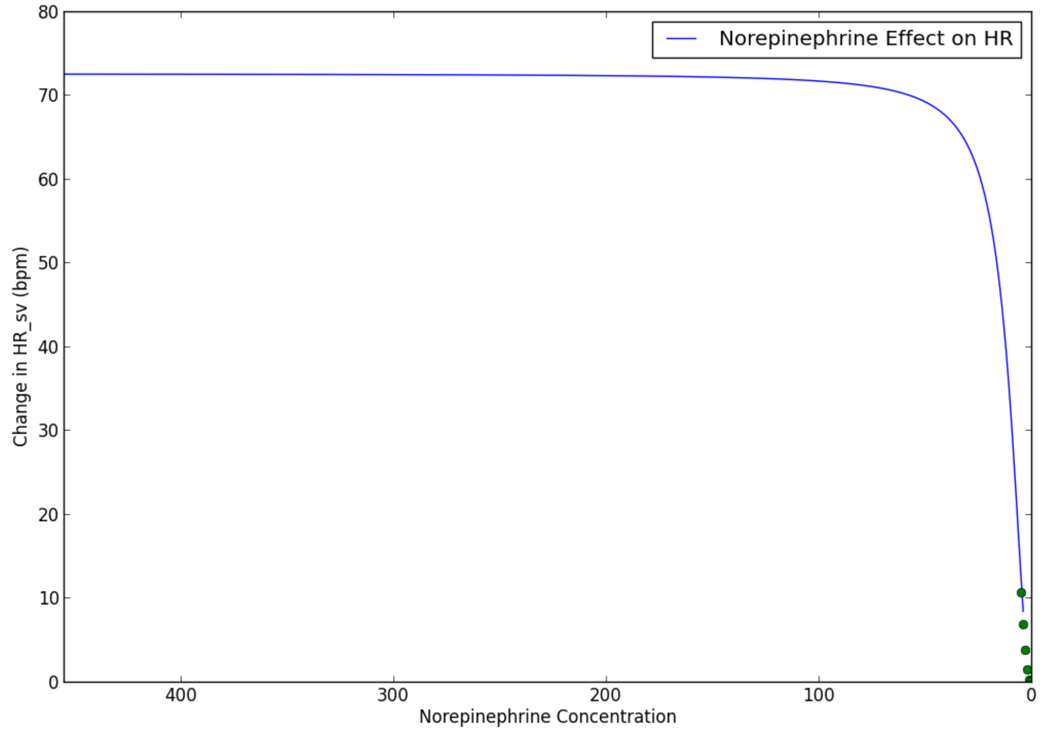


Fig. 2

From this updated model and the equations provided above, a distribution showing the change in heart rate due to norepinephrine can be performed. Via final_project_pinckney.py, the results of such a distribution can be seen in the graph below:



The blue line respresents the range of concentration levels that Mokrane and Nadeau used for analysis. The green dots represent a completion of the analysis through total depletion of norepinephrine. As one can see from the graph above, once norepinephrine concentration hits around 50 concentration units, norepinephrine's effect on HR_{sv} starts to diminish greatly. And concentrations higher than 50 units have relatively the same effect on HR_{sv}, holding a pretty constant rate of change of about 72.5bpm.

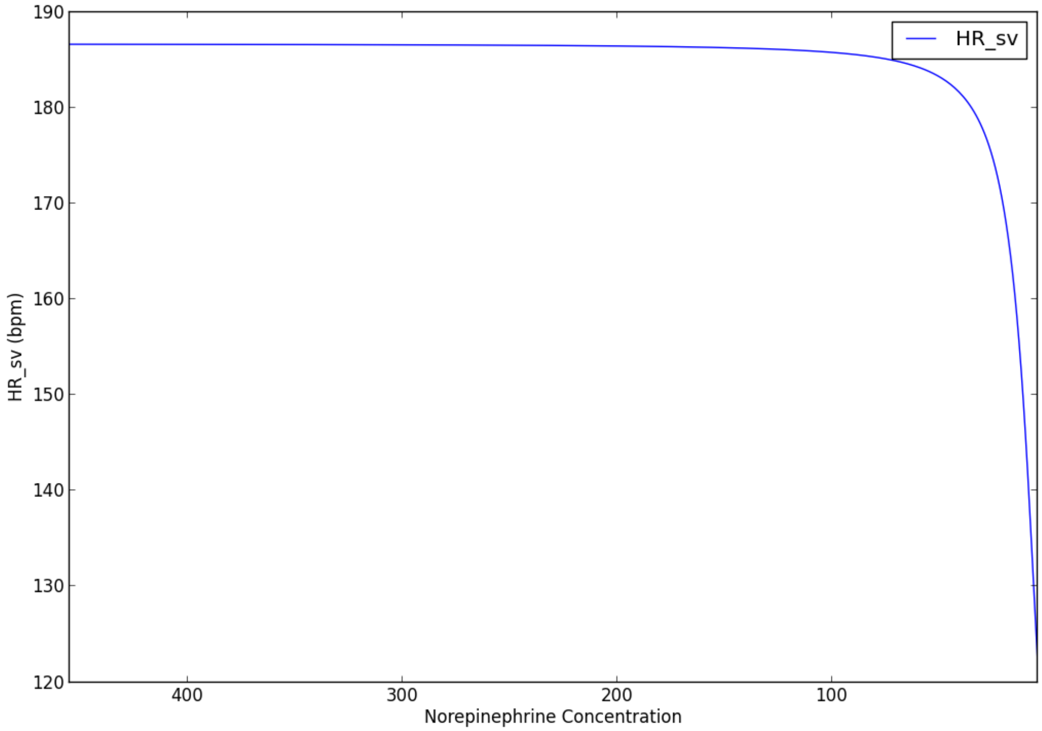
Now, let's put both the parasympathetic and sympathetic nervous system models together and see which one wins out over HR_{sv}!

$HR_{sv} = HR_v + (HR_s - HR_0)\ (HR_v - HR_{min})/(HR_0 - HR_{min})$,
where: HR_0 = 110bpm and
HR_{min} = 30bpm.

Let's assume that: $HR_{s\_i} = \Delta HR + HR_{sv\_i-1}$ for time = i and
$HR_{v\_i} = 2.125 + HR_{sv\_i-1}$ for time = i
(2.125 = slope calculated via final_project_pinckney.py)

Therefore:
$HR_{sv\_i} = (2.125 + HR_{sv\_i-1}) + ((\Delta HR + HR_{sv\_i-1}) - HR_0)\ ((2.125 + HR_{sv\_i-1}) - HR_{min})/(HR_0 - HR_{min})$,

Solving for HR_{sv}, the following is generated by final_project_pinckney.py:



As one can clearly see, the introduction of norepinephrine caused the individual in this simulation to increase their heart rate from 110bpm to about 187bpm, which appears to represent a threshold. And the sympathetic nervous system won out over the parasympathetic nervous system, at least until the norepinephrine concentration reached about 90 concentration units. At which point, the parasympathetic nervous system wielded more control over heart rate causing it to drop.

Further Research:
Given that many aspects of this complicated system have been left out or treated as constants, further research endeavors would include adding these aspects into the model and analyzing those results.

[All of this is hosted on my github account: https://github.com/rpinckney/fight-and-flight.]

References:

"Module 7.6: Cardiovascular System – A Pressure-Filled Model"
Shiflet & Shiflet

"Effect of Combined Sympathetic and Vagal Stimulation on Heart Rate in the Dog"
By Homer R. Warner, M.D., Ph.D., and Richard O. Russell, Jr., M.D.
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"Dynamics of heart rate response to sympathetic nerve stimulation"
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