Heroin Model
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April 18, 2018

Background

The misuse of opioids, a drug class including prescription pain relievers and the illegal drug heroin, is rampant in today's society. The opioid crisis was declared a public health emergency in October 2017 by the United States Department of Health and Human Sciences [15]. In 2016, there were 11.8 million opioid misusers 12 years of age or older with 948,000 of these being heroin users [10]. In addition, there was an estimated 13,219 heroin deaths in 2016, a more than six-fold increase from the year 2002 [7]. This, in part, is due to the recent trend of lacing heroin with fentanyl, a surgical-grade opioid that is up to fifty times more potent than heroin alone, and therefore, users are unaware of the purity of the heroin they obtain [12, add in another source later].

Prescription pain relievers are misused for a variety of reasons with the most prominent being to relieve physical pain, to feel good or get high and to relax or relieve tension. Individuals that misuse prescription opioids mostly obtain them from friends/relatives or from a healthcare provider, with misuse defined as taking the prescription at a higher dose or more frequently than prescribed, or taking someone else's medication [10].

To address this apparent problem in today's society, we have formulated a population level model to investigate the dynamics among individuals taking prescription opioids, addicted to opioids, using heroin and recovering from opioid and/or heroin addiction. Opioids are of no shortage in society today. The number of prescriptions that pharmacies distributed in 2011 was almost triple that of 1991 and there is a higher availability of heroin in recent years at a lower cost than alternative opioids. This leads some individuals to start heroin [14]. We aim to find ways to optimally treat pain with prescriptions while reducing opioid addiction and heroin use. This model was motivated by a previous model focusing solely on opioid addicts through prescriptions or via the black market; the purpose of formulating a separate model is to be able to understand the more complicated dynamics that arise among opioid abuse and heroin use [1].

Model Formulation

Our model consists of five subgroups of the national population:

1. Susceptibles (S): This portion of the population consists of individuals who are not taking prescription opioids of any kind, nor are using heroin.

2. Prescription opioid users (P): This class of individuals consists of individuals who are prescribed opioids by a health care provider and take the opioids as recommended by their doctor, so they are not considered addicted.

3. Opioid addicts (A): This group of individuals are addicted to opioids. Although

the opioid class of drug includes heroin, here we will take opioids to mean non-heroin. In addition, opioid misuse, abuse and addiction will be used interchangeably throughout.

4. Heroin users (H): This class is composed of individuals who use heroin, which is implicitly understood to be addictive.

5. Individuals in treatment/rehabilitation (R): This class consists of individuals undergoing treatment for their addiction to opioids and/or heroin.

We denote the initial conditions as $S(0) = S_0$, $P(0) = P_0$, $A(0) = A_0$, $H(0) = H_0$, and $R(0) = R_0$, and we assume all of these values are positive. From data, the initial values for each of the classes are the following proportions of the entire population: $S_0 = 0.6221$, $P_0 = 0.37$, $A_0 = 0.0062$, $H_0 = 0.0014$, and $R_0 = 0.0003$ [4, add in others later].
*Will show that starting with positive initial conditions, will stay positive for all time.

Here, we present our ordinary differential equation model:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha S - \beta(1-\xi)SA - \beta\xi SP - \theta_1 SH + \epsilon P + \delta R + \mu(P+R) + (\mu+\mu_A)A + (\mu+\mu_H)H \quad (1)$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha S - \epsilon P - \gamma P - \theta_2 PH - \mu P \quad (2)$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \gamma P + \sigma_A R + \beta(1-\xi)SA + \beta\xi SP - \zeta A - \theta_3 AH - (\mu+\mu_A)A \quad (3)$$

$$\frac{\mathrm{d}H}{\mathrm{d}t} = \theta_1 SH + \theta_2 PH + \theta_3 AH + \sigma_H R - \nu H - (\mu+\mu_H)H \quad (4)$$

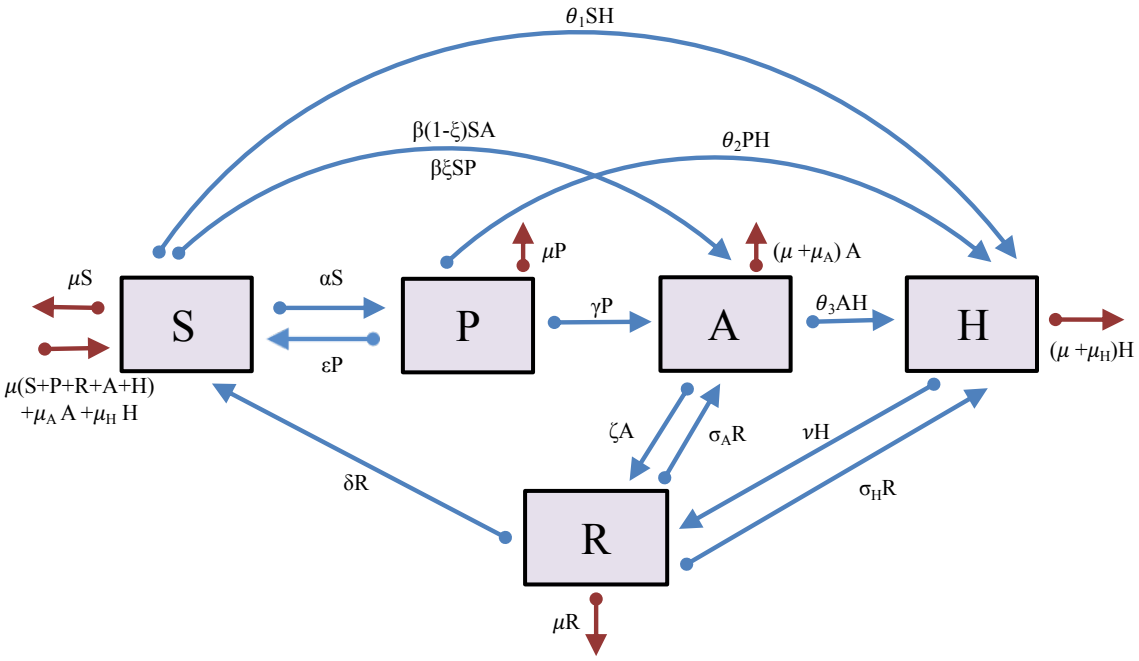
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \zeta A + \nu H - \delta R - \sigma_A R - \sigma_H R - \mu R \quad (5)$$

The parameters involved in this model represent transition rates from one class to another; specifically:

- α: the rate at which individuals are prescribed opioids
- β : total probability of becoming addicted to opioids by some means other than prescription
- $\beta(1-\xi)$: proportion of the susceptible population that becomes addicted to opioids by black market drugs or interaction with other addicts
- $\beta\xi$: proportion of the susceptible population that obtains extra prescription opioids and becomes addicted
- θ_1: rate at which the susceptible population becomes addicted to heroin by black market availability or interaction with other heroin users
- ϵ: rate at which people come back to the susceptible class after being prescribed opioids and did not develop an addiction

- δ: rate at which people enter back into the susceptible class after successfully finishing treatment
- μ: natural death rate
- μ_A: enhanced death rate for opioid addicts (overdose rate which results in death)
- μ_H: enhanced death rate for heroin addicts (overdose rate which results in death)
- γ: rate at which prescribed opioid users become addicted to opioids
- θ_2: rate at which prescribed opioid users become addicted to heroin
- σ_A: rate at which individuals relapse from treatment back into the opioid addicted class
- ζ: rate at which addicted opioid users enter treatment/rehabilitation
- θ_3: rate at which the opioid addicted population becomes addicted to heroin
- σ_H: rate at which individuals relapse from treatment into the heroin addicted class
- ν: rate at which heroin users enter treatment/rehabilitation

This compartmental model can be represented by the following flow diagram with each arrow representing either the transition rate between one class to another or death:



Equilibrium Analysis

To find the addiction-free equilibrium, we set equations (1)-(5) equal to zero and require that $A = H = R = 0$. We are left with the system:

$$0 = -\alpha S^* - \beta\xi S^* P^* + \epsilon P^* + \mu P^*$$
$$0 = \alpha S^* - \epsilon P^* - \gamma P^* - \mu P^*$$
$$0 = \gamma P^* + \beta\xi S^* P^*$$

If $P = 0$, then the only solution is $S^* = P^* = H^* = R^* = 0$. Thus, will assume P $\neq 0$. This forces $\gamma + \beta\xi S^* = 0$ and since all of our parameters and variables are non-negative, then it must be $\gamma = 0$ and either $\beta = 0$ or $\xi = 0$. Under the assumption that $\gamma = 0 = \xi$ to ensure the existence of our AFE and that $1 = S+P+A+H+R$, we calculate the AFE to be

$$S^* = \frac{\epsilon + \mu}{\alpha + \epsilon + \mu}$$
$$P^* = \frac{\alpha}{\alpha + \epsilon + \mu}$$
$$A^* = 0$$
$$H^* = 0$$
$$R^* = 0$$

Basic Reproduction Number, $\mathscr{R}_0$

For the purposes of calculating $\mathscr{R}_0$, we will assume $\gamma = 0$ and $\xi = 0$ (thus, $\beta \neq 0$) in order to ensure the existence of the addiction-free equilibrium. This results in the infected compartment (3)-(5) reducing to:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \sigma_A R + \beta SA - \zeta A - \theta_3 AH - (\mu + \mu_A)A$$
$$\frac{\mathrm{d}H}{\mathrm{d}t} = \theta_1 SH + \theta_2 PH + \theta_3 AH + \sigma_H R - \nu H - (\mu + \mu_H)H$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \zeta A + \nu H - \delta R - \sigma_A R - \sigma_H R - \mu R$$

Thus, under the assumption of A, H and R as the infected compartments and parameter restrictions stated above, the assumptions of the Next Generation Method are satisfied for matrices $\mathscr{F}$ and $\mathscr{V}$ shown below. Note that $\mathscr{F}_i$ represents the rate that secondary infections enter infected compartment i and $\mathscr{V}_i$ represents the difference between the rate of transfer out of compartment i and the rate of transfer into compartment i by means different than a secondary infection. Using this method results in the following matrices:

$$\mathscr{F} = \begin{pmatrix} 0 \\ 0 \\ \beta SA \\ \theta_1 SH + \theta_2 PH \\ 0 \end{pmatrix}$$

$$\mathscr{V} = \begin{pmatrix} \alpha S + \beta SA + \theta_1 SH - \epsilon P - \delta R - \mu(P + R + A + H) - \mu_A A - \mu_H H \\ -\alpha S + \epsilon P + \theta_2 PH + \mu P \\ -\sigma_A R + \zeta A + \theta_3 AH + (\mu + \mu_A)A \\ -\theta_3 AH - \sigma_H R + \nu H + (\mu + \mu_H)H \\ -\zeta A - \nu H + \delta R + \sigma_A R + \sigma_H R + \mu R \end{pmatrix}$$

$$F = \begin{pmatrix} \beta S^* & 0 & 0 \\ 0 & \theta_1 S^* + \theta_2 P^* & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \zeta + \mu + \mu_A & 0 & -\sigma_A \\ 0 & \nu + \mu + \mu_H & -\sigma_H \\ -\zeta & -\nu & \delta + \sigma_A + \sigma_H + \mu \end{pmatrix}$$

The eigenvalues of FV^{-1} are calculated to be:

$$\sigma(FV^{-1}) = \{0, \frac{(r+s)-\sqrt{(r-s)^2+4\beta S^* z\sigma_A\zeta\sigma_H\nu}}{2det(V)}, \frac{(r+s)+\sqrt{(r-s)^2+4\beta S^* z\sigma_A\zeta\sigma_H\nu}}{2det(V)}\}$$

$\mathscr{R}_0$ may then be determined as the spectral radius of FV^{-1}:

$$\mathscr{R}_0 = \frac{(r+s)+\sqrt{(r-s)^2+4\beta S^* z\sigma_A\zeta\sigma_H\nu}}{2det(V)}$$

where $a = \zeta + \mu + \mu_A$, $b = \nu + \mu + \mu_H$, $c = \delta + \sigma_A + \sigma_H + \mu$, $z = \theta_1 S^* + \theta_2 P^*$, $r = \beta S^*(bc - \sigma_H\nu), s = z(ac - \sigma_A\zeta)$, and $det(V) = a(bc - \sigma_H\nu) - \sigma_A\zeta b$.

We note that the radicand $(r-s)^2 + 4\beta S^* z\sigma_A\zeta\sigma_H\nu$ is positive, since all parameters are positive. In addition, r is positive since bc contains the term that cancels with $-\sigma_H\nu$, s is positive since ac contains the term that cancels with $-\sigma_A\zeta$ and finally, $det(V)$ is positive since abc contains terms that cancel with $-\sigma_A\zeta(\nu + \mu + \mu_H) - \sigma_H\nu$.

Sensitivity Analysis

In order to explore the sensitivity of each of the population classes to each of the parameters, we implemented Sobol sensitivity analysis in which the Saltelli sampler is utilized to generate N(2D+2) parameter samples where N=FILL IN is the number of sample points and D=16, the number of parameters in the model for a total of FILL IN samples [16].

Saltelli are the statistically good points chosen in the parameter space to test and records S, P, A, H and R at the final time (t=10 years) for the parameter choices. Samples N points from the problem and returns a matrix of parameter values.

Both μ_A and μ_H were restricted to the domain $[0, 0.1]$ with the remaining parameters ranging on the entire domain $[0, 1]$. For first-order indices, only one parameter is varied and the rest are held constant; for second-order indices, two parameters are varied and the rest are held constant; and for total-order indices, every combination of parameters is varied, from a single parameter varying alone to all higher-order interactions between parameters. The length of the colored bars, with each color representing a specific class, measures the contribution of a certain parameter to the variance of each of the classes in the model. The longer the colored bar, the higher the effect the parameter has on that class of individuals. We are able to retrieve the confidence intervals on the sensitivity of each of the populations to a respective change in the parameter(s) for first order changes, second order changes and total order changes.

**Takes the mean from the last 100 (or 10 for the case of t=10) time steps. (I thought final time??)
**Total –take average of all interactions for plots??
**Need to scale sensitivities of muA and muH based on their domain $[0, 0.1]$??

References

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