Modelling the Opioid Epidemic in New York

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Procedure Break-down

Goal: Model the Prescription Opioid Epidemic for New York City and New York State excluding NYC, compare the impact of the parameters on the different outcomes.

1. History of epidemiology
2. Prescription opioid model
3. Sensitivity analysis
4. Results

References

- **Battista, N.A., Pearcy, L.B. & Strickland, W.C. "*Modeling the Prescription Opioid Epidemic.*" Bull Math Biol (2019) 81: 2258. https://doi.org/10.1007/s11538-019-00605-0**
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The Opioid Epidemic

- More than 130 people die every day from opioid overdose
- Dangerous uptrend of death caused by opioid overdose since 1990
- Prescription misuse accounted for **78.5 billion** a year in U.S
- **11.4 million** people misused prescription opioids in 2017
- A large amount of people become Opioid-dependent because of severe accidents such as car crash
- Overdose death more than doubled from 2007 to 2017

Why We Care: The Opioid Epidemic in NYS

- Roland: Had own experience with opioids, consulting (can include pharma companies)
- Noah: Medicine, public health, data driven treatment
- Simon: Investment in pharmaceutical stocks

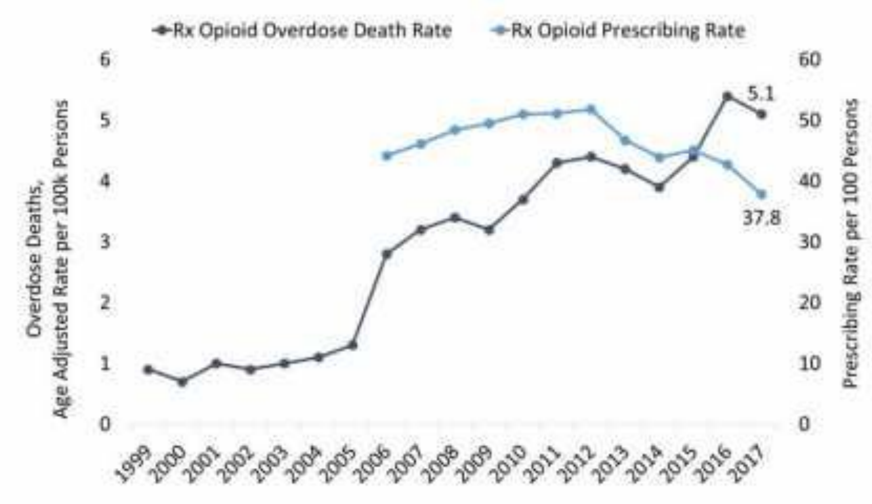
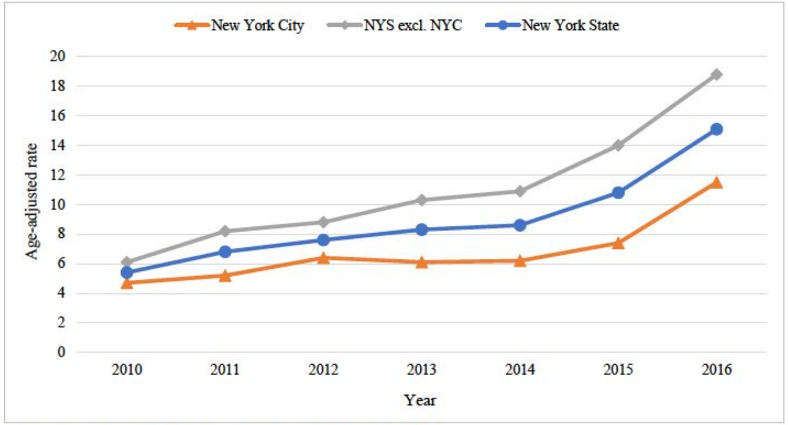


Figure 1.5 Overdose deaths involving any opioid, age-adjusted rate per 100,000 population, by region, New York State, 2010-2016



Data source: CDC WONDER; Data accessed August 2018

Why NYC vs NYS

- Urban/Rural divide in the opioid epidemic
- Ability to keep most other factors (geographic, etc) equal
- Difference could mean that different approaches are needed for different demographics

History of Epidemiology

Definition: Epidemiology is the study of the distribution and determinants of public health events in specified populations.

Application cases:

1. *Elimination of smallpox*
   - Dr. Edward Jenner first discovered that cowpox infected milkmaids are immune to smallpox in 1796
   - eventually established the theory of vaccine in 1801
   - Mankind eradicated this devastating disease in 1997
2. *Tobacco and lung cancer*
   - found direct causations between smoking and lung cancer
   - helped push the law to mandate the label “smoking can kill you” on cigarette cases in 1965

The last patient of smallpox

Mathematical Methods in Epidemiology: A Timeline

(**1927**) Kermack and McKendrick:

- Introduce the original SIR model
- Focus on causal factors in contagious epidemics

(**1979**) Anderson and May:

- Use population dynamics to explore spread of infectious diseases

(**2007**) White and Comiskey:

- Revise model to address heroin epidemic in Ireland

(**2019**) **Battista, Pearcy, Strickland:**

- Apply model to prescription opioid epidemic in the US
- Formulated to address addiction

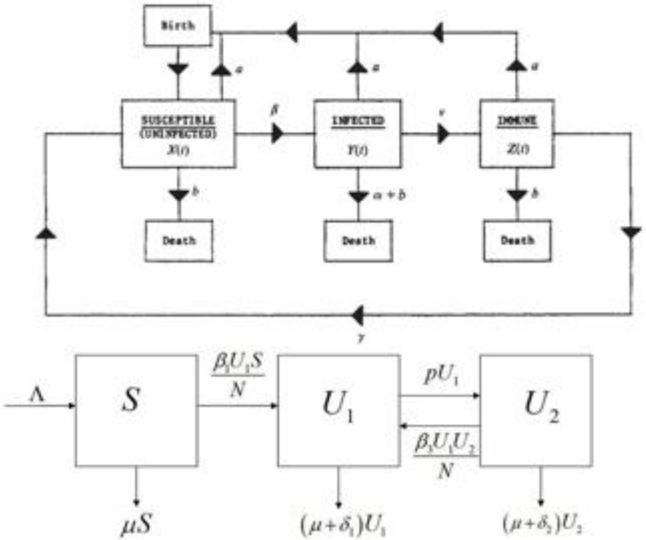


Figure: SIR model (top) and revised model for heroin use (bottom)

Prescription Opioid Model

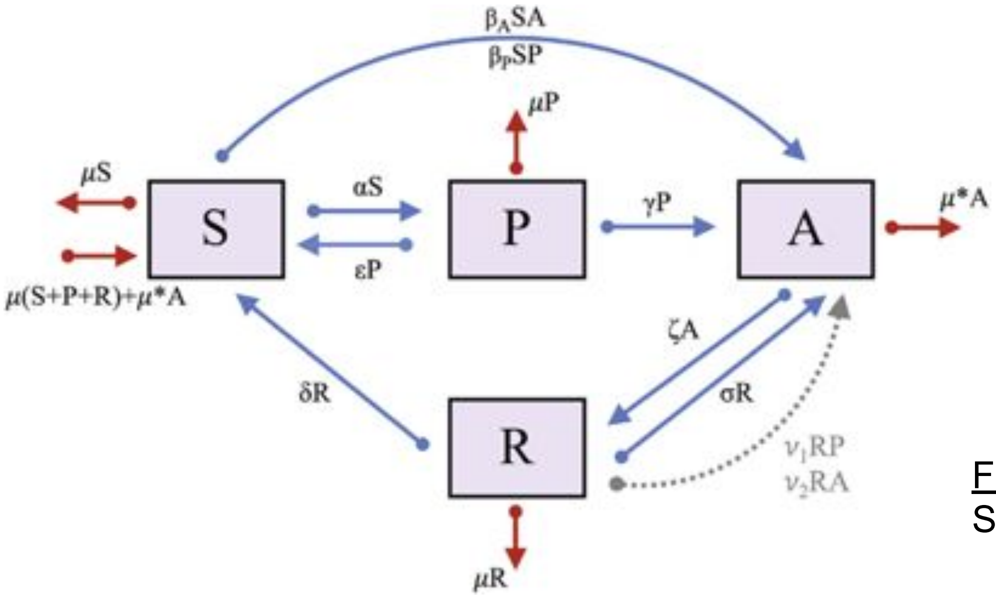


Figure: Battista, Pearcy, and Strickland's population model

Prescription Opioid Model

- Four different population classes:
  - ‘**S**’: Susceptible
  - ‘**P**’: Prescribed Users
  - ‘**A**’: Addicted*
  - ‘**R**’: Rehabilitation/Treatment
- Assumptions for population model:
  1. $S + P + R + A = 1 \, \forall t$
  2. $\dot{S} + \dot{P} + \dot{R} + \dot{A} = 0 \, \forall t$
  3. $S, P, R, A \geq 0 \, \forall t$

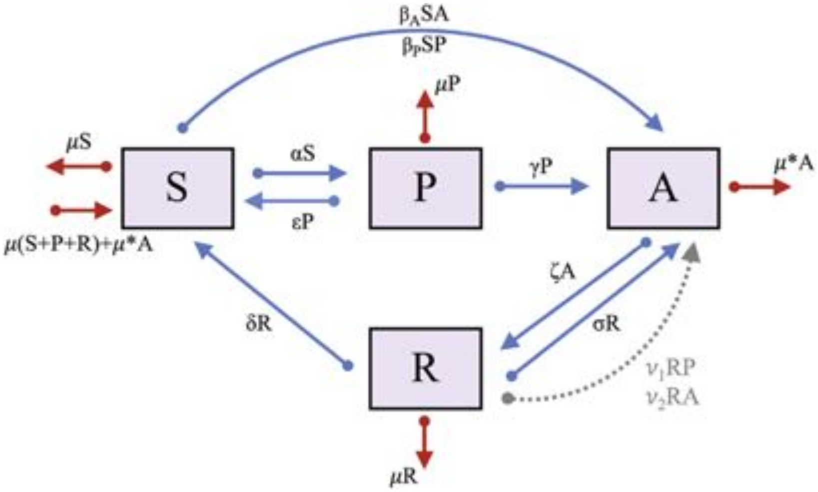
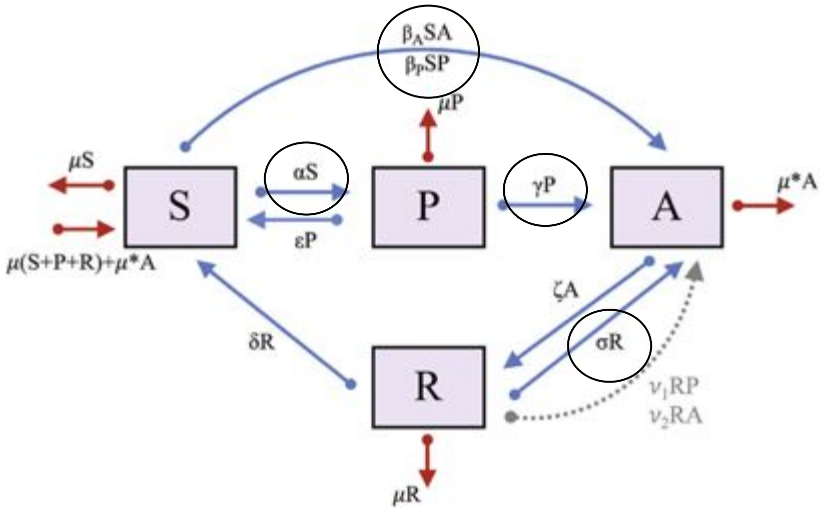


Figure: Battista, Pearcy, and Strickland’s population model

* : ‘Addicted’ here refers to the proportion of the population with an opioid related Substance Abuse Disorder (SUD)

Prescription Opioid Model: Flow from S to A

- **α**: Prescription rate
- **γ**: Addiction rate
- **β**: Addiction rate via illicitly obtained opiates:
  - $\beta_{\mathbf{A}}$: Addiction rate via <u>addict-sourced</u> prescription opiates
  - $\beta_{\mathbf{p}}$: Addiction rate via <u>prescription-sourced</u> prescription opiates
  - Depend on existing populations A and P, respectively
- **σ**: Relapse rate



<u>Figure:</u> Battista, Pearcy, and Strickland's population model

Prescription Opioid Model: Flow from A to S

- **ε:** End prescription without addiction rate
- **ζ:** Treatment entry rate
- **δ:** Treatment success rate

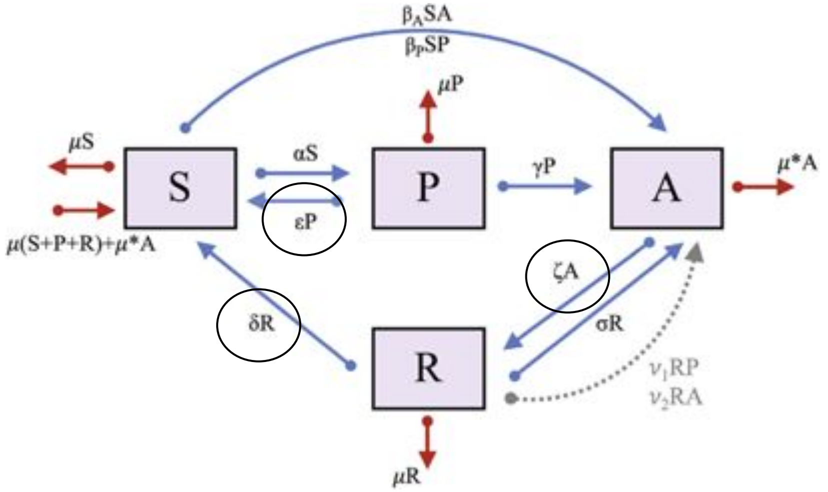


Figure: Battista, Pearcy, and Strickland’s population model

Prescription Opioid Model: Satisfying Assumptions

- μ / μ^* : Natural death rate and the addicted death rate.
- Returns all deaths back into the model at S to maintain $S + P + R + A = 1 \; \forall t$

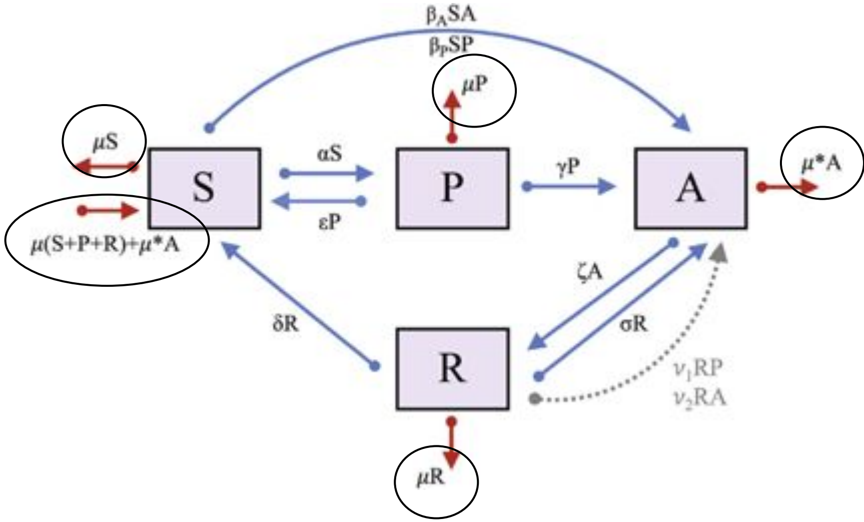
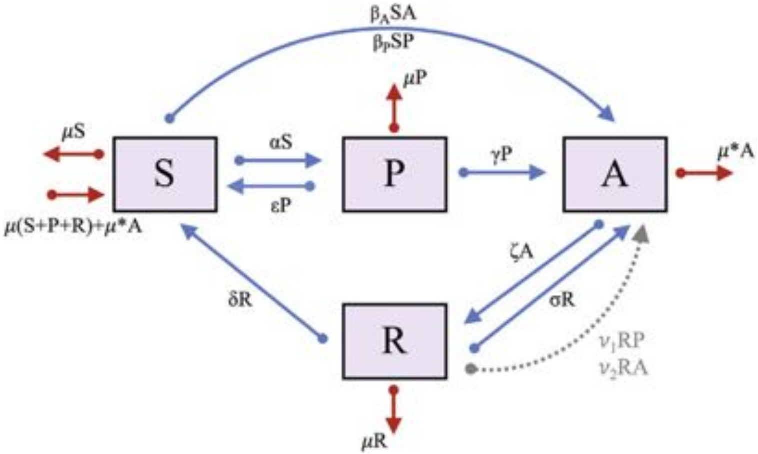


Figure: Battista, Pearcy, and Strickland's population model

Prescription Opioid Model: 5-D Dynamical System



- Can be expressed as four time-continuous differential equations:

$$(1)\ \dot{S} = -\alpha S - \beta_A SA - \beta_P SP + \varepsilon P + \delta R + \mu(P + R) + \mu^* A$$
$$(2)\ \dot{P} = \alpha S - (\varepsilon + \gamma + \mu)P$$
$$(3)\ \dot{A} = \gamma P + \sigma R + \beta_A SA + \beta_P SP - (\zeta + \mu^*)A$$
$$(4)\ \dot{R} = \zeta A - (\delta + \sigma + \mu)R$$

Prescription Opioid Model: Model Validation Method

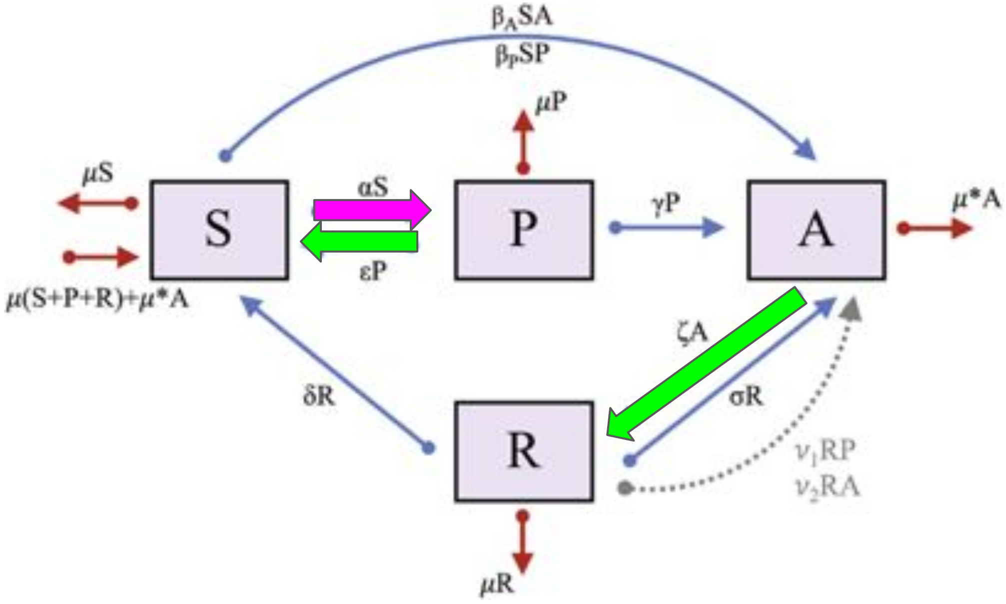
I. Input parameters calculated from sourced data.
   - Values from various levels of the population: sub state, state, regional, and national
   - Manipulated to reflect yearly rates of change
   - **'Realistic' parameters, not real parameters**
   - Varying values for 'difficult' parameters
     - Prescription rate
     - Rate of completing prescription without addiction
     - Treatment entry rate
   - Input data for overall population numbers, as well as all opioid OD deaths for 2010-2017
     - Calculate <u>Addicted Opioid-Related Deaths</u> $ORD_A(t)$

Prescription Opioid Model: Model Validation Method

I. Input parameters calculated from sourced data.

II. Solve ODE’s for 2010-2017:

- Solve for combinations of α,ε,ζ
- Adaptive RK4 solver



Prescription Opioid Model: Model Validation Method

- Scaling to minimize data-sourced parameters:

1) $\dot{S} = -\alpha S - \beta_A SA - \beta_P SP + \varepsilon P + \delta R + \mu(P+R) + \mu^* A$
2) $\dot{P} = \alpha S - (\varepsilon + \gamma + \mu)P$
3) $\dot{A} = \gamma P + \sigma R + \beta_A SA + \beta_P SP - (\zeta + \mu^*)A$
4) $\dot{R} = \zeta A - (\delta + \sigma + \mu)R$

1) $\dot{s} = -(\alpha + a + p)s + \frac{(\epsilon+\mu)}{k}p + \alpha\left(\frac{1}{\sigma} - 1\right)r + \frac{\mu^*}{g}a$
2) $\dot{p} = \alpha ks - (\epsilon + \gamma + \mu)p$
3) $\dot{a} = \alpha gr + (h\gamma + gs)p + \big(gs - (\zeta + \mu^*)\big)a$
4) $\dot{r} = \frac{\zeta\sigma}{\alpha g}a - r$

Assumptions and Definitions:

- $\delta + \sigma + \mu = 1$
- $t = \tau * (\delta + \sigma + \mu)^{-1}$
- $S = \frac{s}{\alpha}$
- $P = \frac{p}{\beta_P}$
- $A = \frac{a}{\beta_A}$
- $R = \frac{r}{\sigma}$
- $h = \frac{\beta_A}{\beta_p}$
- $k = \frac{\beta_p}{\alpha}$
- $g = \frac{\beta_\alpha}{\alpha} = h * k$

Prescription Opioid Model: Adaptive RK45

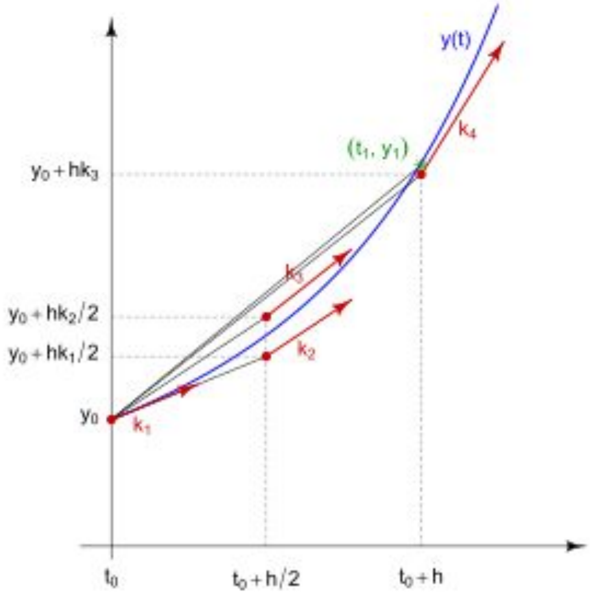
- Fourth Order Runge-Kutta-Fehlberg:

$$for\ \vec{X}_n = \begin{bmatrix} S_{(t_n)} \\ P_{(t_n)} \\ A_{(t_n)} \\ R_{(t_n)} \end{bmatrix} and\ \ \vec{F}(t_n, \vec{X}_n) = \begin{bmatrix} \dot{S} \\ \dot{P} \\ \dot{A} \\ \dot{R} \end{bmatrix}:$$

$$Let\ \vec{X}_{n+h} = \vec{X}_n + \vec{K} + O(h^5)\ such\ that:$$

- $\vec{K}_1 = h * \vec{F}(t_n, \vec{X}_n)$
- $\vec{K}_2 = h * \vec{F}\left(t_n + \frac{h}{2}, \vec{X}_n + \frac{\vec{K}_1}{2}\right)$
- $\vec{K}_3 = h * \vec{F}\left(t_n + \frac{h}{2}, \vec{X}_n + \frac{\vec{K}_2}{2}\right)$
- $\vec{K}_4 = h * \vec{F}(t_n + h, \vec{X}_n + \vec{K}_3)$

- $\vec{K} = \frac{\vec{K}_1 + \vec{K}_4}{6} + \frac{\vec{K}_2 + \vec{K}_3}{3}$



Prescription Opioid Model: Model Validation Method

I. Input parameters calculated from sourced data.

II. Solve ODE's for 2010-2017:

- Solve for combinations of α,ε,ζ
- Adaptive time step fourth order Runge Kutta (RK4)
- Calculate simulated opioid related addict deaths $ORD_S(t)$
  - $ORD_S(t) = population(t) * [A(t) * (\mu^* - \mu)]$
  - Proportion of addict deaths attributed to opioid related causes for year t
- Find $d(S, A) := |ORD_S(t) - ORD_A(t)|$

Prescription Opioid Model: Model Validation Method

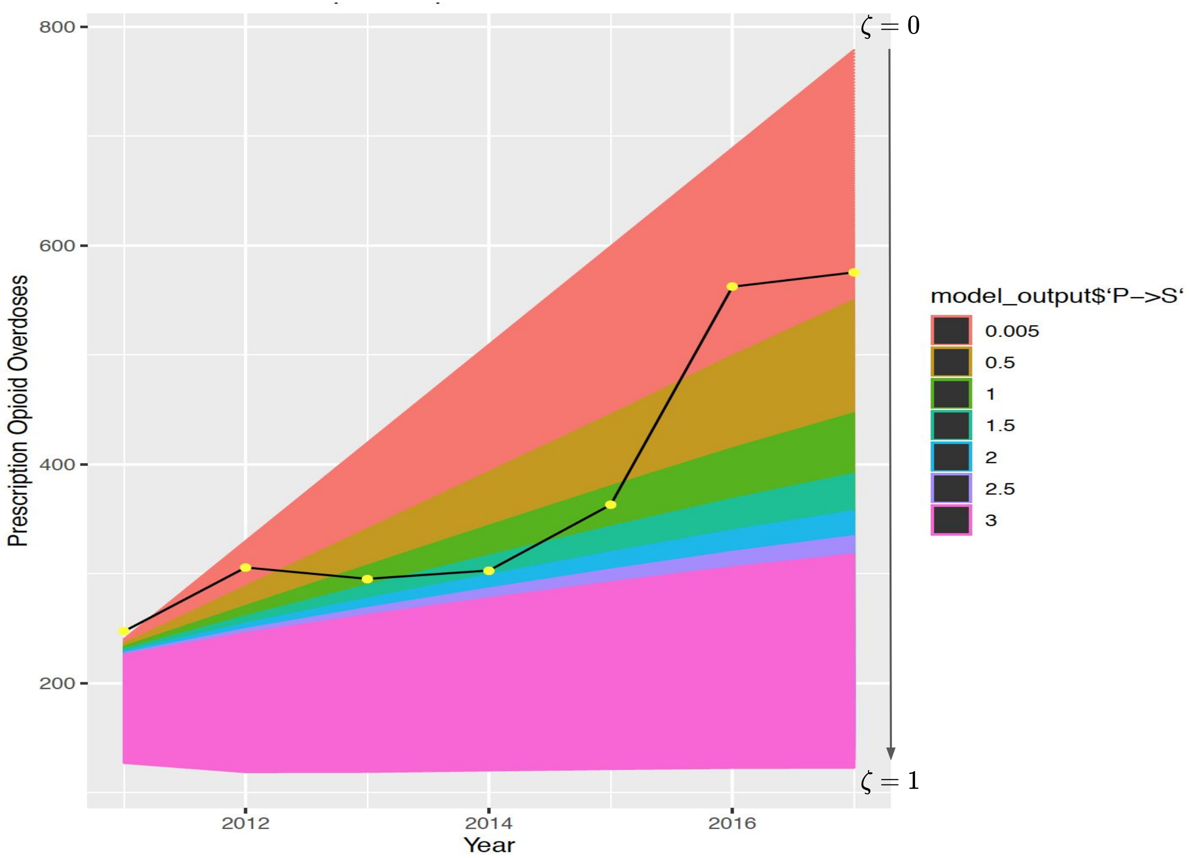
I. Input parameters calculated from sourced data.

II. Solve ODE's for 2010-2017

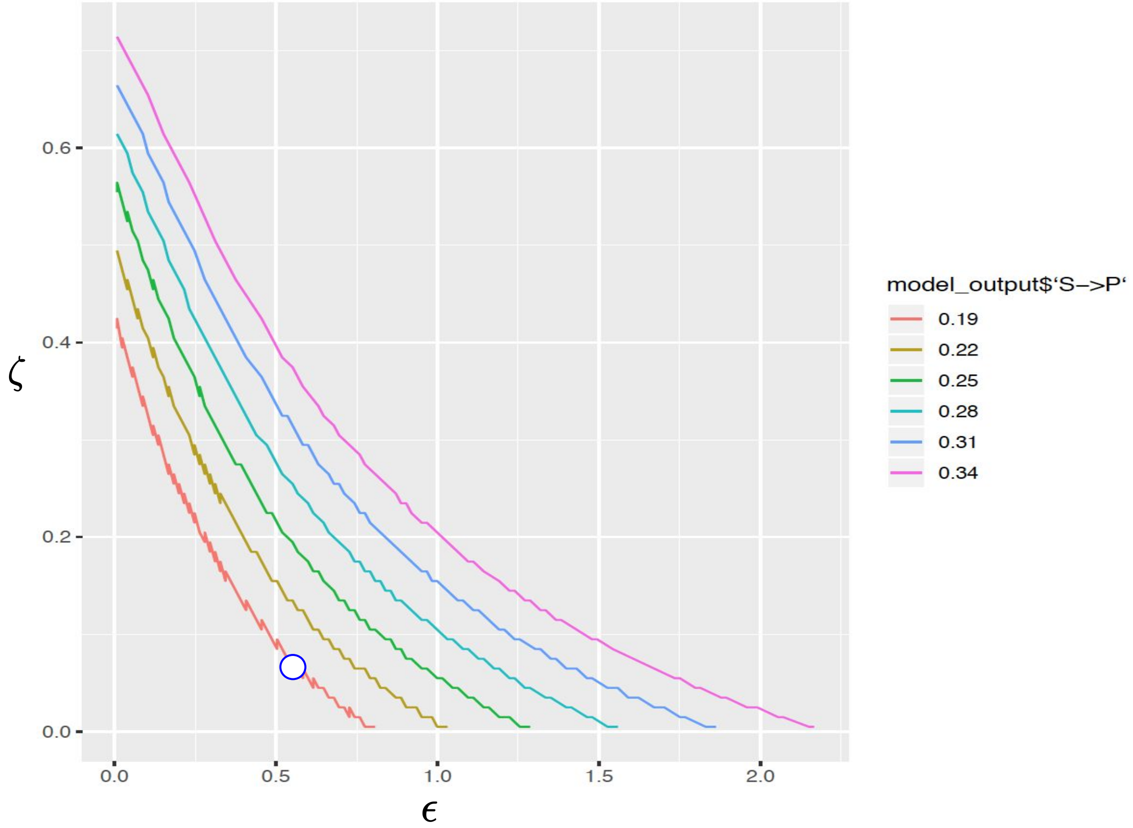
III. Output Findings: Can we find realistic results?

- $ORD_S(t)$ vs. Year
- α,ε,ζ resulting in minimal d(S,A)

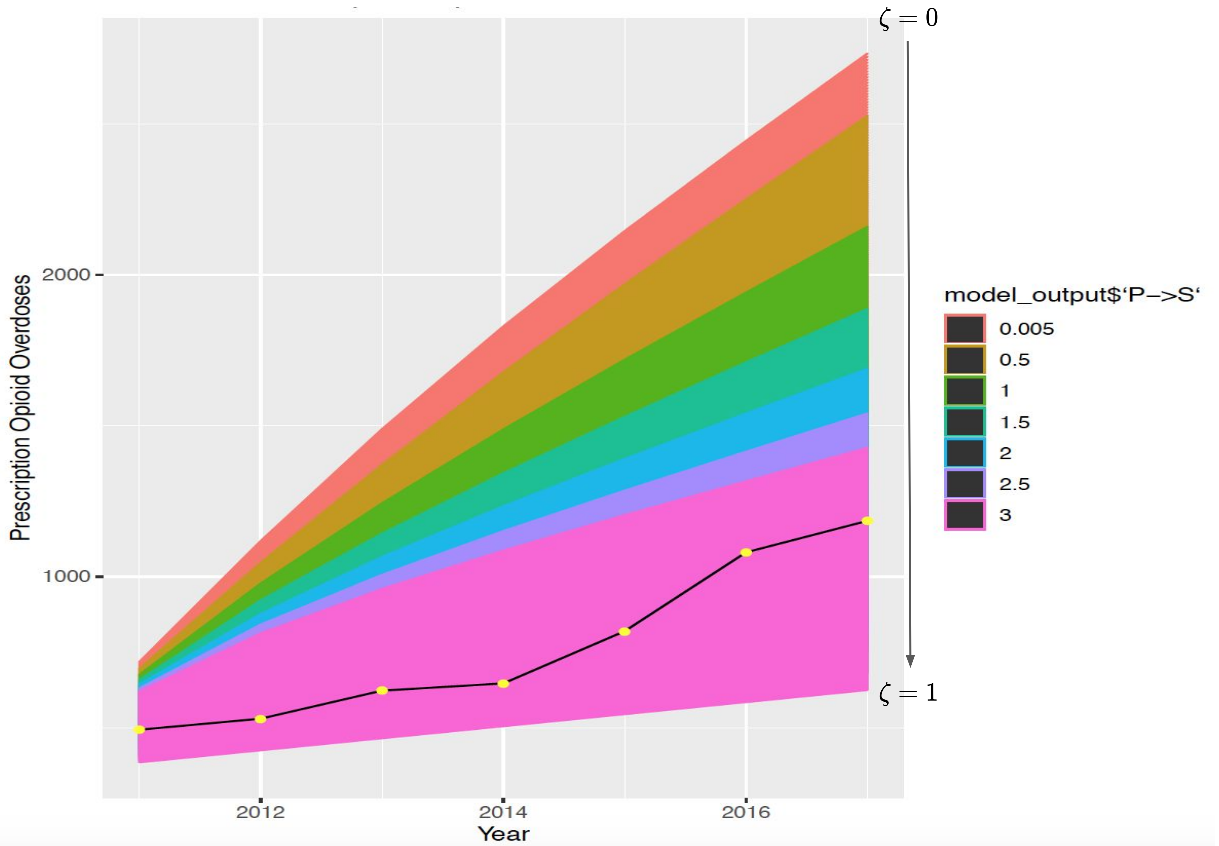
NYC Results: Simulated Deaths per Year



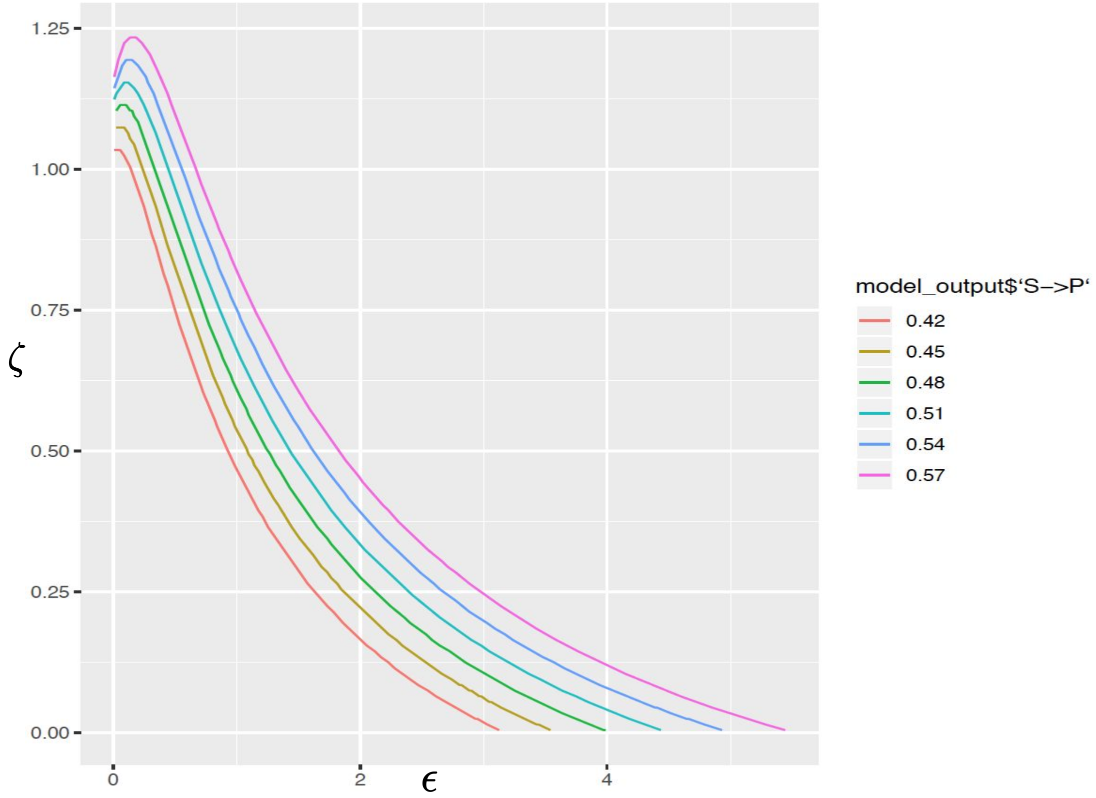
NYC Results: Parameter Plot



NYS\NYC Results: Simulated Deaths per Year

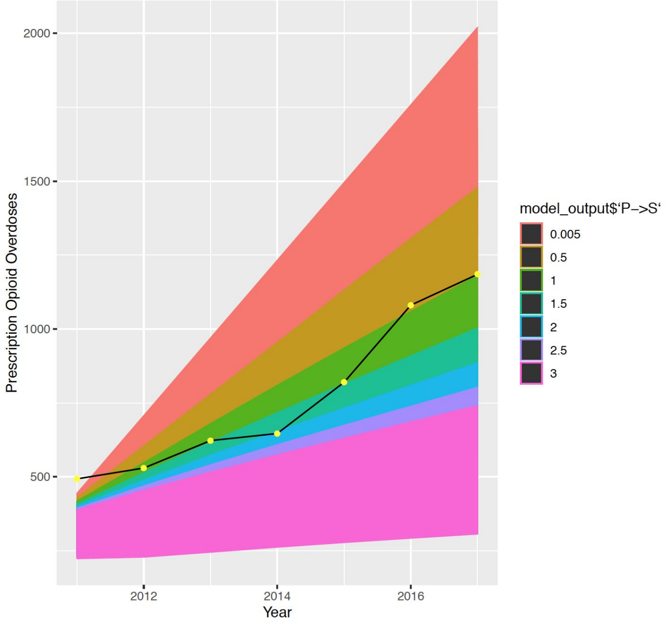


NYS\NYC Results: Parameter Plot



Variance Based Sensitivity Analysis

- Range of outcomes is still too wide
- What is the relative <u>impact</u> of our parameters?
  - Do the two groups react similarly to these factors?
  - If not, what's different?
- **Sensitivity Analysis:** How uncertainty in the output can be attributed to each source
  - Focus on parameter effect on output <u>variance</u>



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Motives & History | Model Overview | Model Validation Method | Sensitivity Analysis and Decomposition Scheme | Monte Carlo and Pseudocode | Results

Sensitivity

I. Scalar Y is a function of all parameters $X_i \ for \ i = 1, 2...k$ such that:
   - $Y = f(X_1, \ldots X_k)$
   - $Var(Y) := V(Y)$ (Uncertainty in the Output)

II. Y can also be defined as a function of X_i such that:
   - $Y = f_i(X_i)$ (Isolated Impact)
   - $Var(Y \ attributed \ to \ X_i) := V_{X_i}(Y)$

Given I and II, can define sensitivity of Y to parameter X_i:

III. $S_i := \frac{V_{X_i}(Y)}{V(Y)}$ (relative sensitivity of Y to Xi)

Functional Decomposition Scheme

- Different order of interactions between parameters
- For $Y = f(X_1, \ldots X_k)$:
  - First order components: $f_i(X_i)$
  - Second order components: $f_{i,j}(X_i, X_j)$
  - And so forth for a total of 2^k terms!
- **Hoeffding Decomposition** of function $Y = f$:

$$f = f_0 + \sum_i f_i + \sum_i \sum_{j>i} f_{ij} + \ldots + f_{12\ldots k}$$

Function Decomposition Scheme: Unicity Condition

- $Considering\,Y\ given\ X_{i_s}\ \forall X_{i_s} \in [0,1]$

$$Y = f_0\ +\ \int_0^1 f_i dx_i\ for\ f_0 = E(Y)\ \iff\ \int_0^1 f_i dx_i = 0$$

- Idea: Components are orthogonal in a K-dimensional space
- **Unicity condition:**

$$\int_0^1 f_{i_1 i_2 \ldots i_s}(X_{i_1}, X_{i_2}, \ldots, X_{i_s})dX_k = 0,\ \text{for}\ k = i_1, \ldots, i_s$$

Function Decomposition Scheme:

- First order case: $Y = f = f_0 + \sum_i f_i$

  $$For\,fixed\,X_i : E_{\mathbf{X_{\sim i}}}(Y\,|X_i) = f_0 + f_i$$

  $$f_0 = E(Y)$$

  $$f_i = E_{\mathbf{X}_{\sim i}}(Y \,\big|\, X_i) - E(Y)$$

- Similarly, for a second order case:

  $$f_{ij} = E_{\mathbf{X_{\sim i,j}}}(Y\,|X_i, X_j) - f_0 - f_i - f_j$$

Functional Decomposition Scheme: Variance

$$f = f_0 + \sum_i f_i + \sum_i \sum_{j>i} f_{ij} + \dots + f_{12\ldots k}$$

Assuming that each f is square integrable,

$$V(f) = \sum_i V_i + \sum_i \sum_{j>i} V_{ij} + \dots + V_{12\ldots k}$$

Considering the first order variance for parameter X_i :

$$V_i = V(f_i) = V_{X_i}\left[E_{\mathbf{X}_{\sim i}}(Y \mid X_i)\right] + V(f_0) = V_{X_i}\left[E_{\mathbf{X}_{\sim i}}(Y \mid X_i)\right]$$

Functional Decomposition Scheme: Variance

- $V_{X_i}[E_{\mathbf{X}_{\sim\mathbf{i}}}(Y \mid X_i)]$: First order variance of output for parameter X_i
- $V_{\mathbf{X}_{\sim\mathbf{i}}}[E_{X_i}(Y \mid \mathbf{X}_{\sim\mathbf{i}})]$: First order variance of output for all parameters EXCEPT X_i
  - Sum of all components independent of X_i
  - Includes first and higher order components
- $V(Y) - V_{\mathbf{X}_{\sim\mathbf{i}}}[E_{X_i}(Y \mid \mathbf{X}_{\sim\mathbf{i}})]$: Total order variance of output depending on X_i
  - Sum of all components dependent on X_i

Functional Decomposition Scheme: Sensitivity

$$\frac{1}{V(f)}\left[V(f) = \sum_i V_i + \sum_i \sum_{j>i} V_{ij} + \ldots + V_{12\ldots k}\right]$$

$$1 = \sum_i S_i + \sum_i \sum_{j>i} S_{ij} + \ldots + S_{12\ldots k}$$

Can define **first and total order sensitivities** of parameter X_i :

$$S_i = \frac{V_{X_i}(E_{X_{\sim i}}(Y|X_i))}{V(Y)}$$

$$S_i^T = \frac{1}{V(Y)}[V(Y) - V_{\mathbf{X}_{\sim\mathbf{i}}}[E_{X_i}(Y \mid \mathbf{X}_{\sim\mathbf{i}})]] = \mathbf{1} - \frac{\mathbf{V}_{\mathbf{X}_{\sim\mathbf{i}}}[\mathbf{E}_{\mathbf{X}_\mathbf{i}}(\mathbf{Y} \mid \mathbf{X}_{\sim\mathbf{i}})]}{\mathbf{V}(\mathbf{Y})}$$

Calculating Sensitivities

Computationally, $V(Y)$ is quite easy. For the others, we have to use a Monte Carlo method:

$$V_{X_i}(E_{\mathbf{X}_{\sim i}}(Y|X_i)) = \frac{1}{N}\sum_{j=1}^{N} f(\mathbf{B})_j(f(\mathbf{A}_{\mathbf{B}}^{(\mathbf{i})})_j - f(\mathbf{A})_j)$$

Where $\mathbf{A}, \mathbf{B}$ are two sampling matrices, and $\mathbf{A}_{\mathbf{B}}^{(\mathbf{i})}$ is $\mathbf{A}$ with the ith row replaced by $\mathbf{B}$.

But how do we know this is the correct method?

Verifying Monte Carlo Method

By Statistical rules, we know that:

$$V(Y) = E(Y^2) - E(Y)^2$$

$E(Y) = \int Y dY$ when probability density is normalized

That means,

$$V_{X_i}(E_{\mathbf{X}_{\sim i}}(Y|X_i)) = \int (E^2_{\mathbf{X}_{\sim i}}(Y|X_i))dX_i - (\int E_{\mathbf{X}_{\sim i}}(Y|X_i)dX_i)^2$$
$$= \int (E^2_{\mathbf{X}_{\sim i}}(Y|X_i))dX_i - E(Y)^2$$

What is $\int (E^2_{\mathbf{X}_{\sim i}}(Y|X_i))dX_i$ and what is $E(Y)^2$?

Verifying Monte Carlo Method

First, $\int E^2(Y|X_j))dx_j$, By definition:

$$\int E^2(Y|X_j))dx_j = \int[\iint \dots \int f(x_1, x_2, \dots x_j, \dots, x_k) \prod_{i=1, i\neq j}^{k} dx_i]^2 dx_j$$

$$= \iint \dots \int f(x_1, x_2, \dots x_j, \dots, x_k) f(x_1', x_2', \dots, x_j, \dots x_k') \prod_{i=1, i\neq j}^{k} dx_i \prod_{i=1, i\neq j} dx_i' dx_j$$

These two sets of variables are going to be calculated using a Monte Carlo method:

$$\int_{\mathbf{R}^\mathbf{m}} f(\mathbf{x}) d\mathbf{x} = \frac{1}{N} \sum_{i=1}^{N} f(\mathbf{x})_i$$

where $\mathbf{x} = (x_1, x_2, \dots, x_m)$, and we take N samples, $(\mathbf{x}_1, \mathbf{x}_2, \dots \mathbf{x}_n)$

Saltelli Sampling

- Sobol quasi-random sequence:
  - A type of sequence that tries to fill an n-dimensional hypercube between [0,1]
  - Designed to make true the statement:

$$\int_{\mathbf{R^m}} f(\mathbf{x})d\mathbf{x} = \frac{1}{N}\sum_{i=1}^{N} f(\mathbf{x})_i$$

  - "Quasi-random" because the sampling tries to fill in spaces where there are no values rather than do it completely randomly
  - Create 3 different matrices using 2N dimensions: $\mathbf{A}, \mathbf{B}, \mathbf{A}_{\mathbf{B}}^{(\mathbf{i})}$

Ten-dimensional Sobol' quasi-random sequence. First eight points.

0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
0.2500	0.7500	0.2500	0.7500	0.2500	0.7500	0.2500	0.7500	0.7500	0.2500
0.7500	0.2500	0.7500	0.2500	0.7500	0.2500	0.7500	0.2500	0.2500	0.7500
0.1250	0.6250	0.8750	0.8750	0.6250	0.1250	0.3750	0.3750	0.8750	0.6250
0.6250	0.1250	0.3750	0.3750	0.1250	0.6250	0.8750	0.8750	0.3750	0.1250
0.3750	0.3750	0.6250	0.1250	0.8750	0.8750	0.1250	0.6250	0.1250	0.8750
0.8750	0.8750	0.1250	0.6250	0.3750	0.3750	0.6250	0.1250	0.6250	0.3750
0.0625	0.9375	0.6875	0.3125	0.1875	0.0625	0.4375	0.5625	0.8125	0.6875

Putting it all together

$\int E^2(Y|X_j))dx_j$ can be seen as the Monte Carlo integration of two sample matrices: $f(\mathbf{B}), f(\mathbf{A_B^{(i)}})$

$E(Y)^2$ can be seen as the Monte Carlo integration of two sample matrices: $f(\mathbf{A}), f(\mathbf{B})$

That is why: $V_{X_i}(E_{\mathbf{X_{\sim i}}}(Y|X_i)) = \frac{1}{N}\sum_{j=1}^{N} f(\mathbf{B})_j(f(\mathbf{A_B^{(i)}})_j - f(\mathbf{A})_j)$

And similarly for total order.

Numerical Sensitivity Analysis - Pseudocode

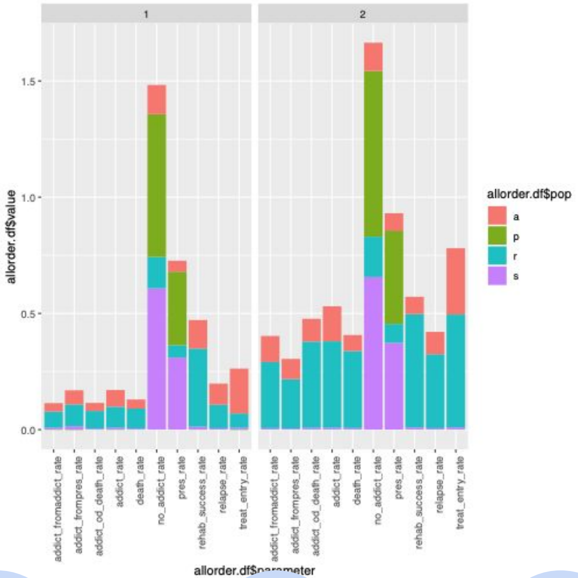
1. Perform sampling to get array for possible combinations of values (e.g. prescription rate between 0.1 and 0.8)
2. Run Sobol Analysis on parameters:
   a. Evaluate all possible combinations through model
   b. Run each output through sobol analysis

$$S_i = \frac{V_{X_i}(E_{X_{\sim i}}(Y|X_i))}{V(Y)}$$ where $$V_{X_i}(E_{\mathbf{X}_{\sim \mathbf{i}}}(Y|X_i)) = \frac{1}{N}\sum_{j=1}^{N} f(\mathbf{B})_j(f(\mathbf{A}_{\mathbf{B}}^{(\mathbf{i})}) - f(\mathbf{A})_j)$$

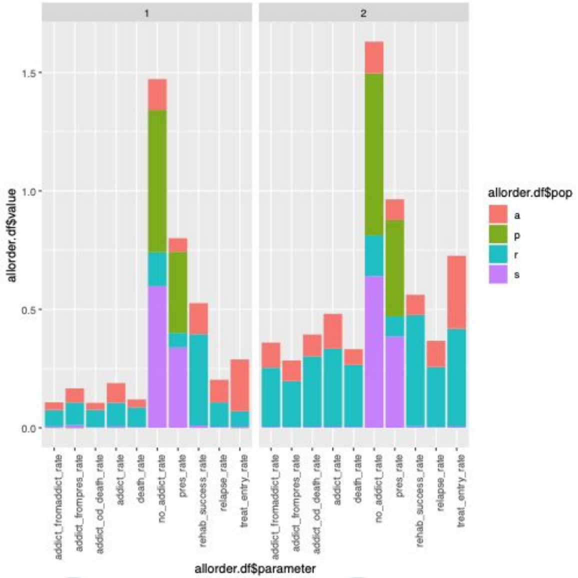
3. Plot Sensitivities

Results:

New York City



New York State excluding NYC



1 Motives & History

2 Model Overview

3 Model Validation Method

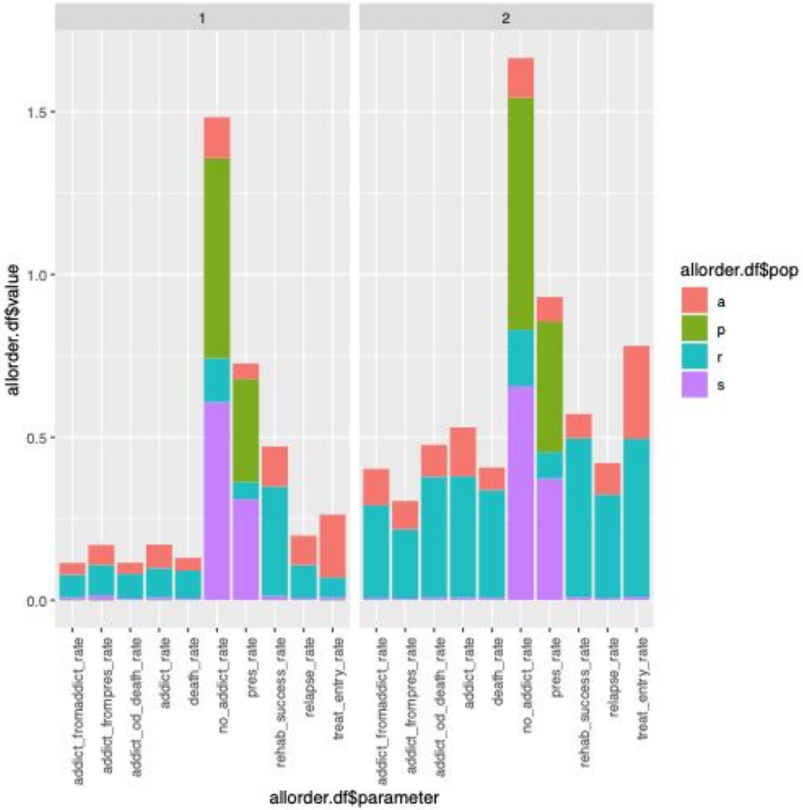
4 Sensitivity Analysis and Decomposition Scheme

5 Monte Carlo and Pseudocode

6 Results

Results: Within Groups

- Both populations are highly sensitive to prescription rates.
- Difference in sensitivity to treatment entry rates hints at non-linear effects.

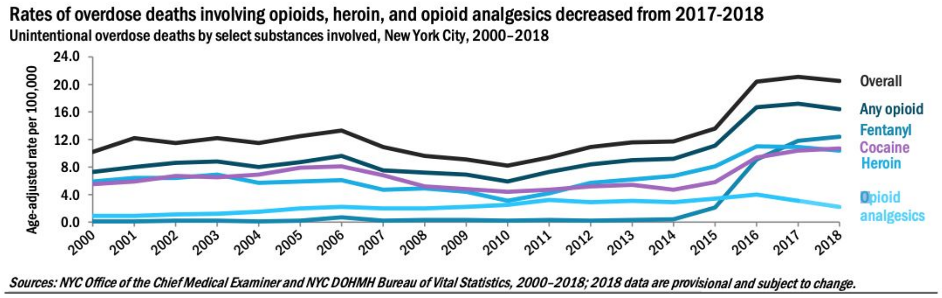


Results: Between Groups

- Comparing distribution of each populations sensitivities between the two sets, tested for no difference.
- Statistically significant (< 0.05) difference between groups for total sensitivity of addicted sub-group to the relapse rate.

Future of the field:

- Focus on fentanyl:
  - ~50-100 x more potent than heroin
  - 60% of overdoses in 2018 (NYC)
  - Most commonly involved in overdoses since 2017 (NYC)
- Focus on smaller communities:
  - HEALing communities study
  - Application of evidence-based treatments
- More data = more and better predictions
  - As more data gets recorded, modelling becomes more accurate and relevant to the field



What’s next for us:

- Roland: Consulting/hopefully never taking opioids again
- Noah: Med school (?)
- Simon: Electronic trading hopefully

- Our future in the field: TBD

Supplement 1: References for Data

- Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. *"Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 national survey on drug use and health."* Ann InternMed. (2015), 167(5):293–302, https://www.ncbi.nlm.nih.gov/pubmed/28761945
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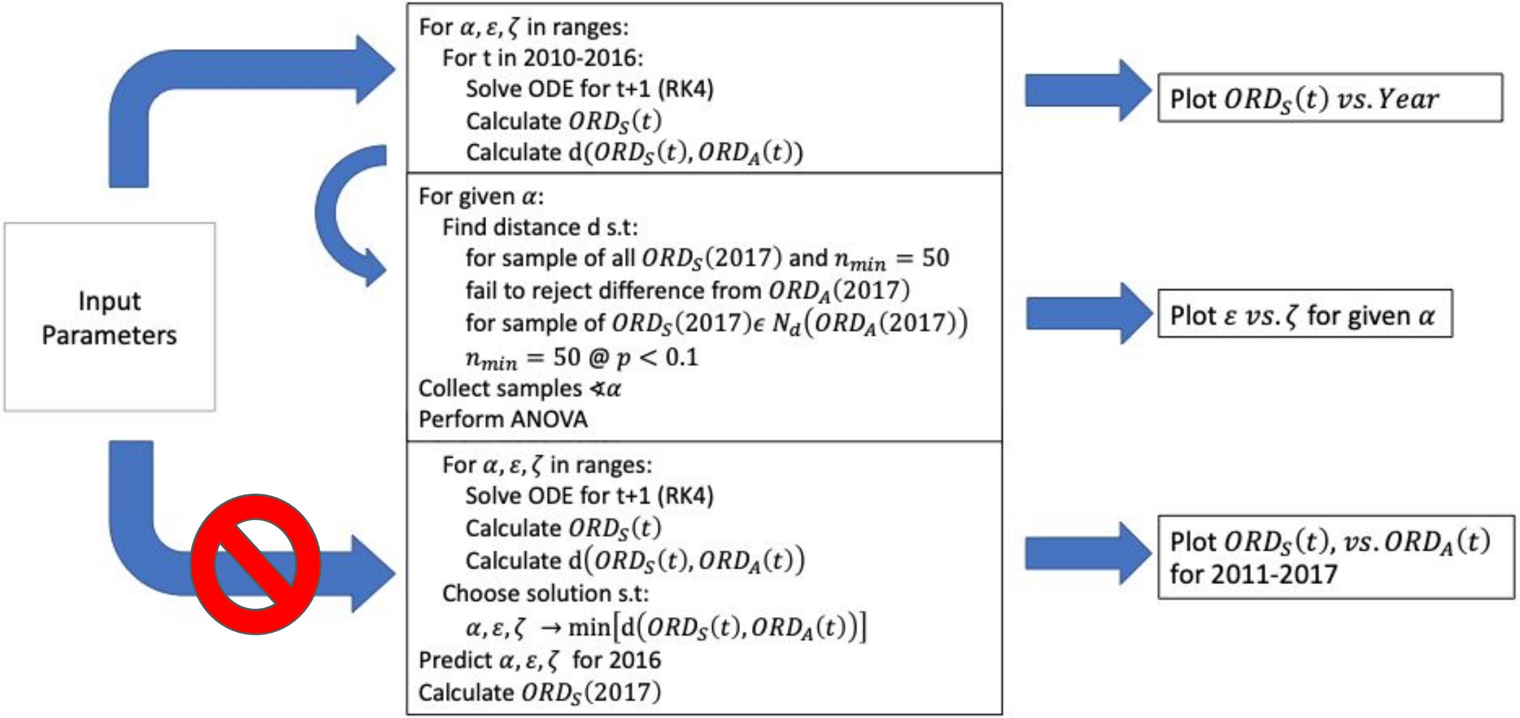
- Vowles KE, McEntee ML, Julnes PS, et al. *"Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis."* Pain. (2015), 156:569–576, https://www.ncbi.nlm.nih.gov/pubmed/25785523

Supplement 2: Opioid Model Overall PseudoCode



Supplement 3: Total Order Monte Carlo

WTF

$$V(Y) - V_{\mathbf{X_{\sim i}}}(E_{X_i}(Y|\mathbf{X}_{\sim i}) = E_{\mathbf{X_{\sim i}}}(V_{X_i}(Y|\mathbf{X}_{\sim i})$$

Where

$$E_{\mathbf{X_{\sim i}}}(V_{X_i}(Y|\mathbf{X}_{\sim i}) = \frac{1}{2N}\sum_{j=1}^{N}(f(\mathbf{A})_j - f(\mathbf{A}_{\mathbf{B}}^{(\mathbf{i})})_j)^2$$

$$= \frac{1}{2}\int [f(x_1, x_2, \dots x_j, \dots, x_k) - f(x_1, x_2, \dots x'_j, \dots x_k)]^2 \prod_{i=1, i\neq j}^{k} dx_i dx_j dx'_j$$

Supplement 3: Continued

$$f(x_1, x_2, \ldots x'_j, \ldots x_k) = f(y', z)$$

$$= \frac{1}{2} \int [f(y, z) - f(y', z)]^2 dz dy' dy$$

$$= \frac{1}{2} \int f^2(\mathbf{x}) d\mathbf{x} + \frac{1}{2} \int f^2(y', z) dy' dz - \int f(\mathbf{x}) f(y', z) d\mathbf{x} dy'$$

$$= \int f^2(\mathbf{x}) d\mathbf{x} - (V_{\mathbf{X}_{\sim i}}(E_{X_i}(Y|\mathbf{X}_{\sim i}) + f_0^2)$$

$$= V(Y) - V_{\mathbf{X}_{\sim i}}(E_{X_i}(Y|\mathbf{X}_{\sim i})$$