

Modeling the Opioid Epidemic

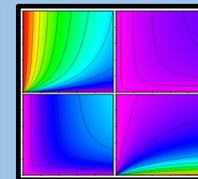
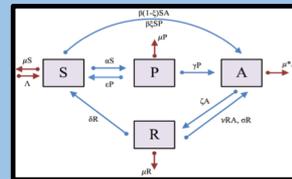
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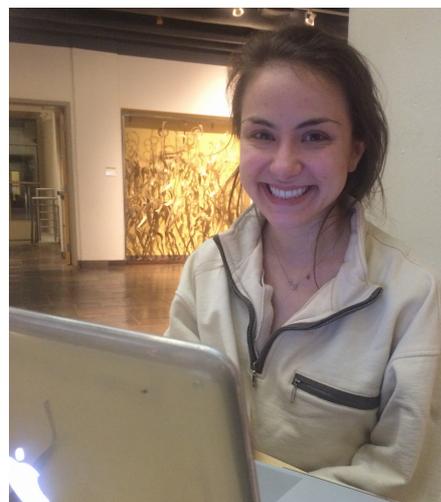
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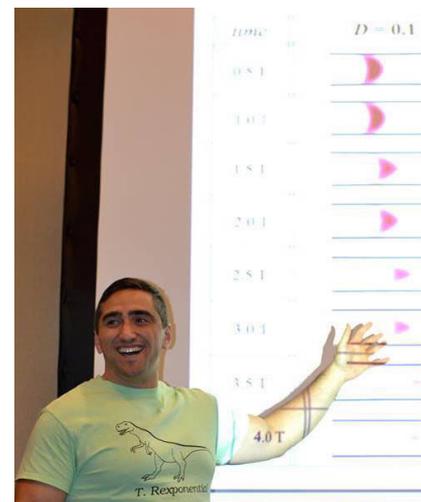
The Opioid Epidemic



Joint work with:

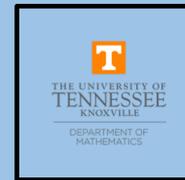
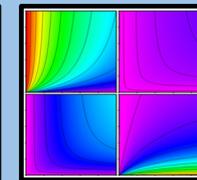
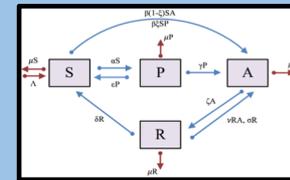


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The Opioid Epidemic

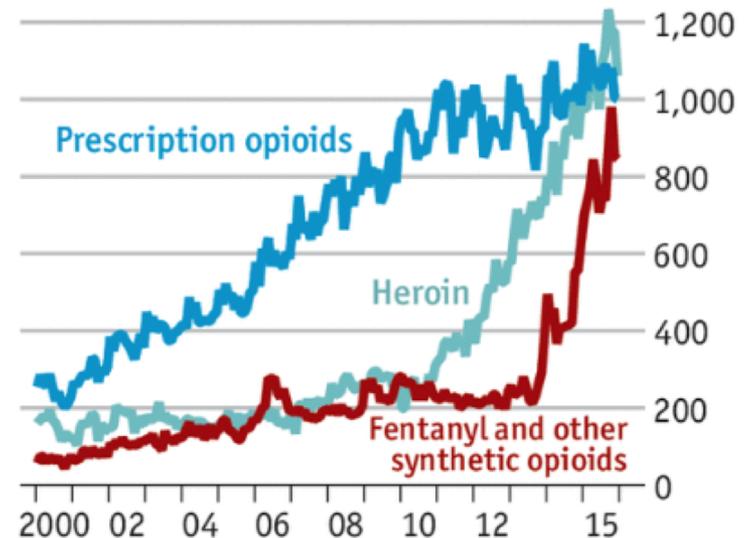


91
AMERICANS

die every day from an **opioid overdose** (that includes prescription opioids and heroin).

New highs

United States, drug overdose deaths*, monthly

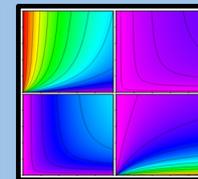
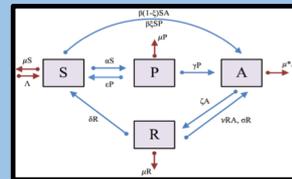


Source: Centres for Disease Control and Prevention

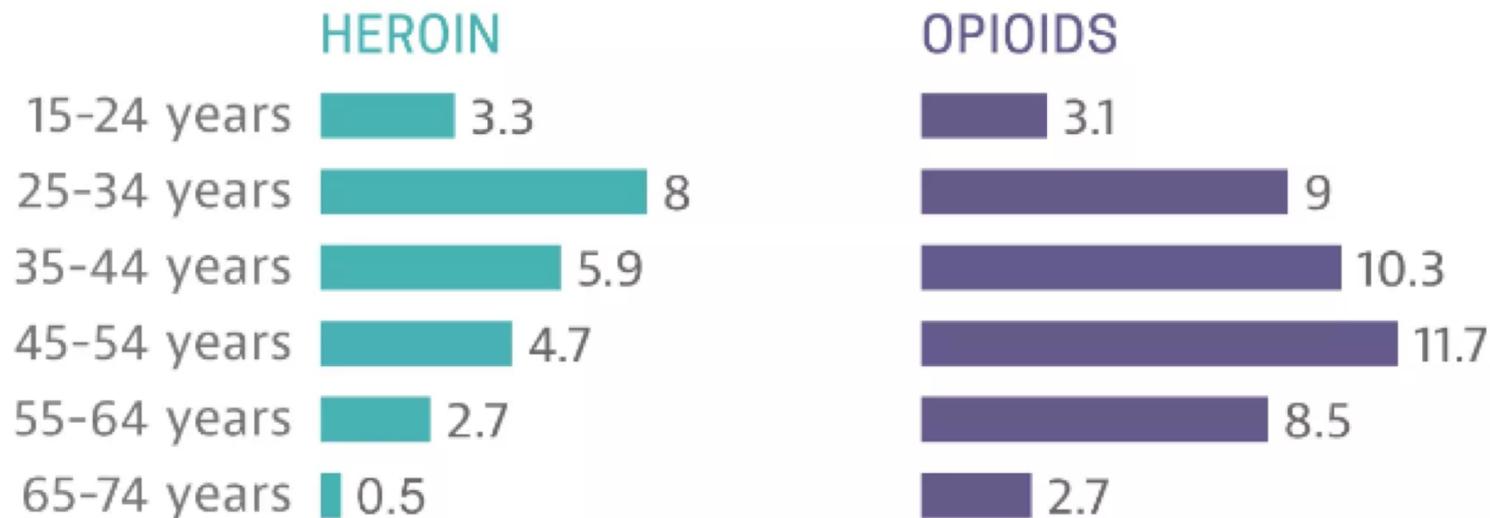
*Deaths involving more than one drug are counted multiple times

Economist.com

The Opioid Epidemic

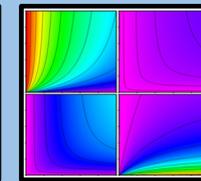
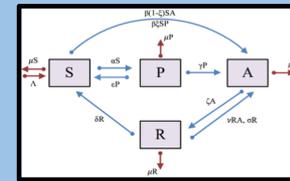


Overdose Deaths by Age in 2014 per 100,000 people



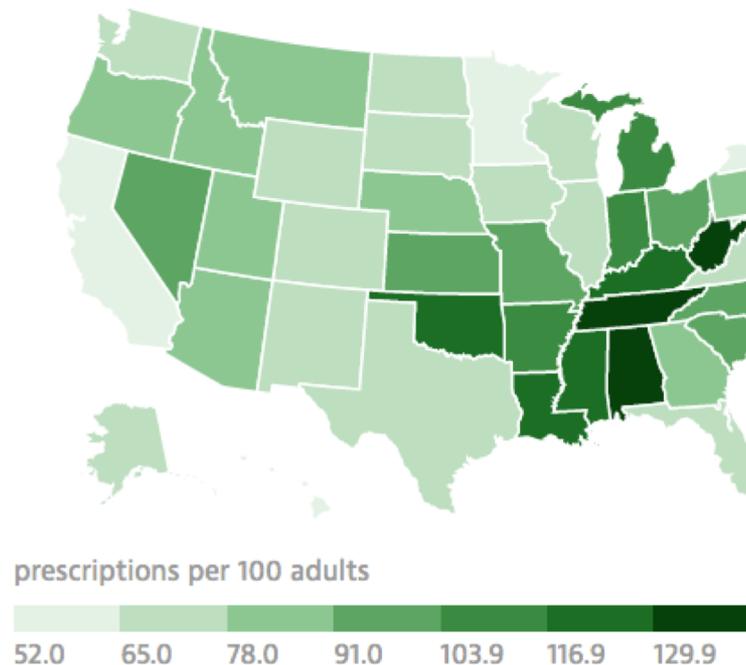
Source: Centers for Disease Control

The Opioid Epidemic



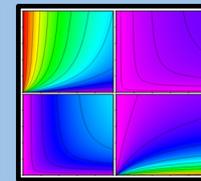
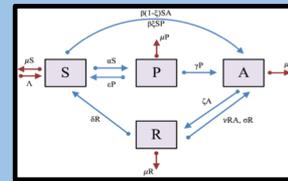
Twelve states have more opioid prescriptions than people

Opioid Pain Reliever Prescriptions by State



Source: Centers for Disease Control

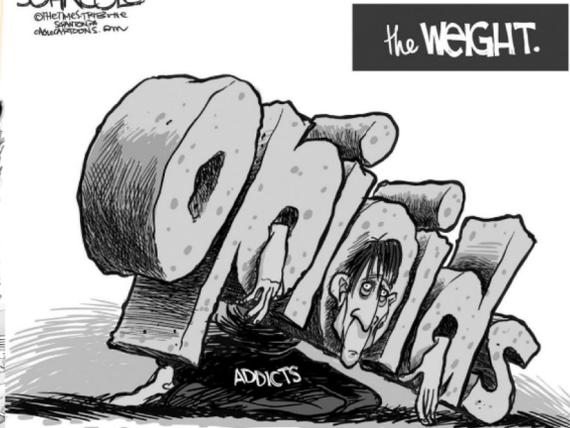
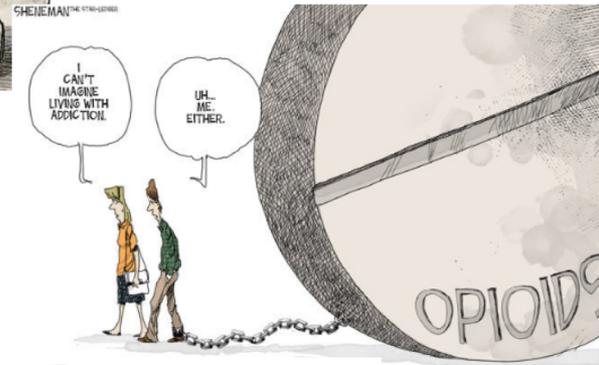
The Opioid Epidemic



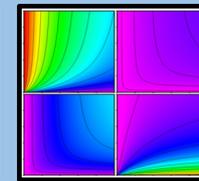
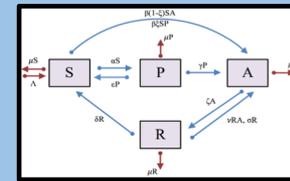
Adam Z



What replaced the neighborhood ice cream truck...



The Opioid Epidemic



Adam Z



What replaced the neighborhood ice cream truck ...

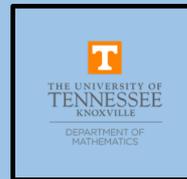
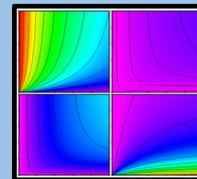
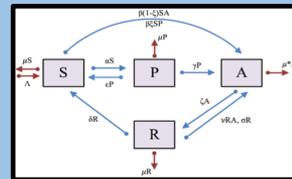


Where are the mathematical models??



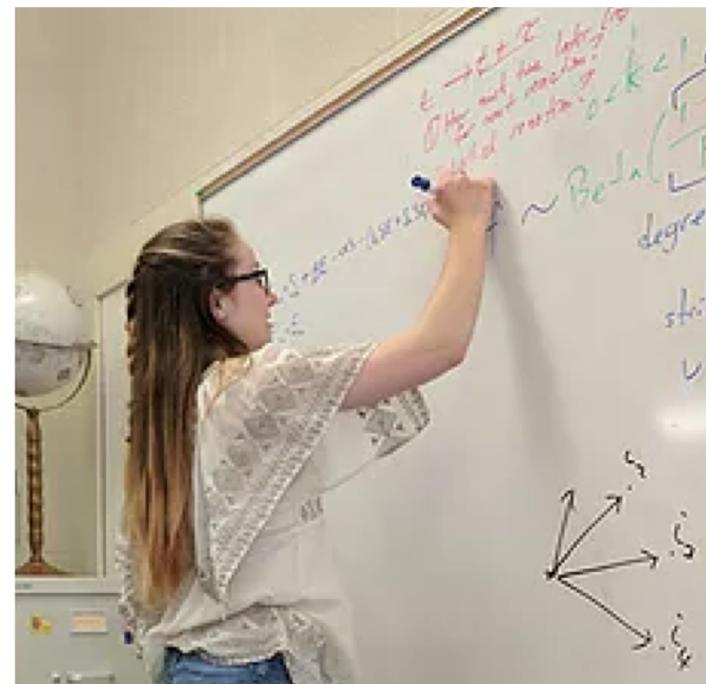
DAVE GRANLUND © www.davegranlund.com

The Opioid Epidemic



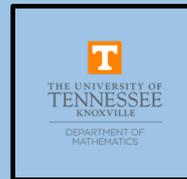
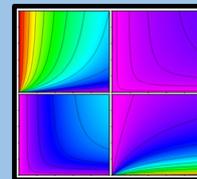
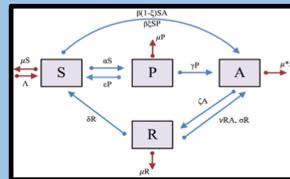
Modeling Goals:

1. **Formulate a first ODE model for prescription opioid addiction**
2. Explore dynamics that make this different from traditional, illicit drug epidemics
3. Analyze the addiction-free state
4. Suggest ways to minimize addiction.



Leigh writing down the first opioid math model

Opioid Epidemic: Model



Four Populations of People

- **S:** *Susceptible* – non-opioid users
- **P:** *Prescribed* – those with prescription opioids
- **A:** *Addicted* – those chronically abusing opioids
- **R:** *Rehabilitation* – those in rehab/treatment

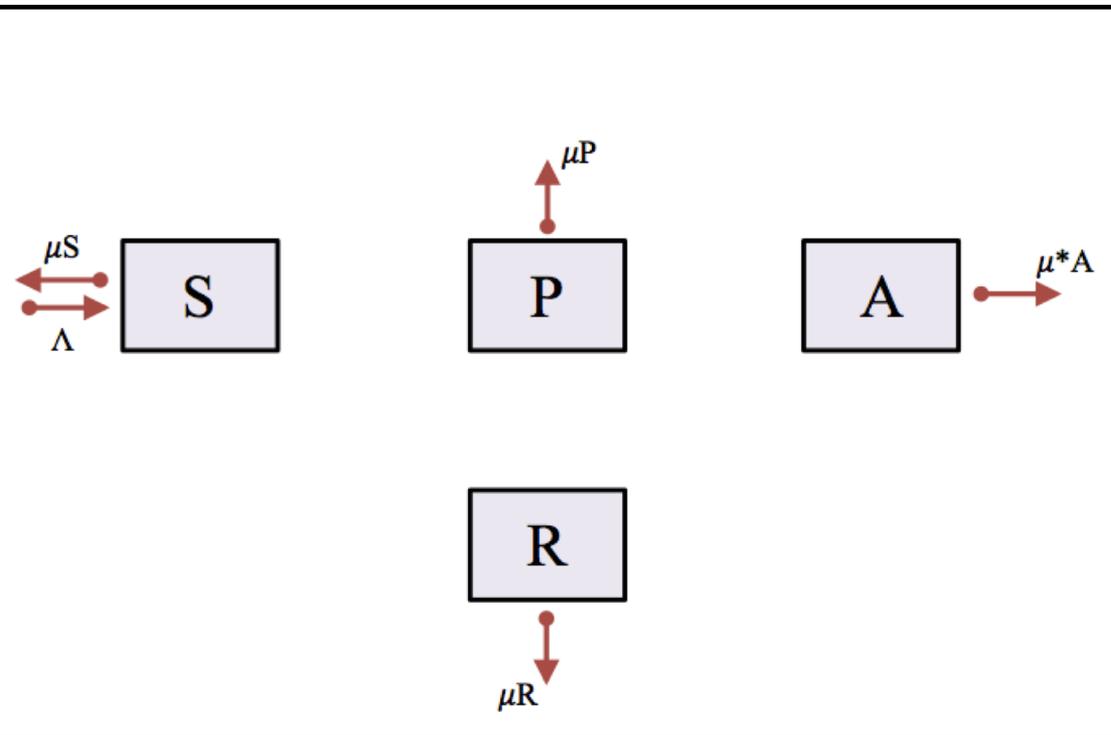
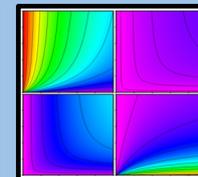
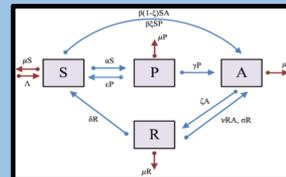
S

P

A

R

Opioid Epidemic: Model



Dynamic: Death Rates

$\left. \begin{matrix} \mu S \\ \mu P \\ \mu R \end{matrix} \right\}$ Typical Death Rate

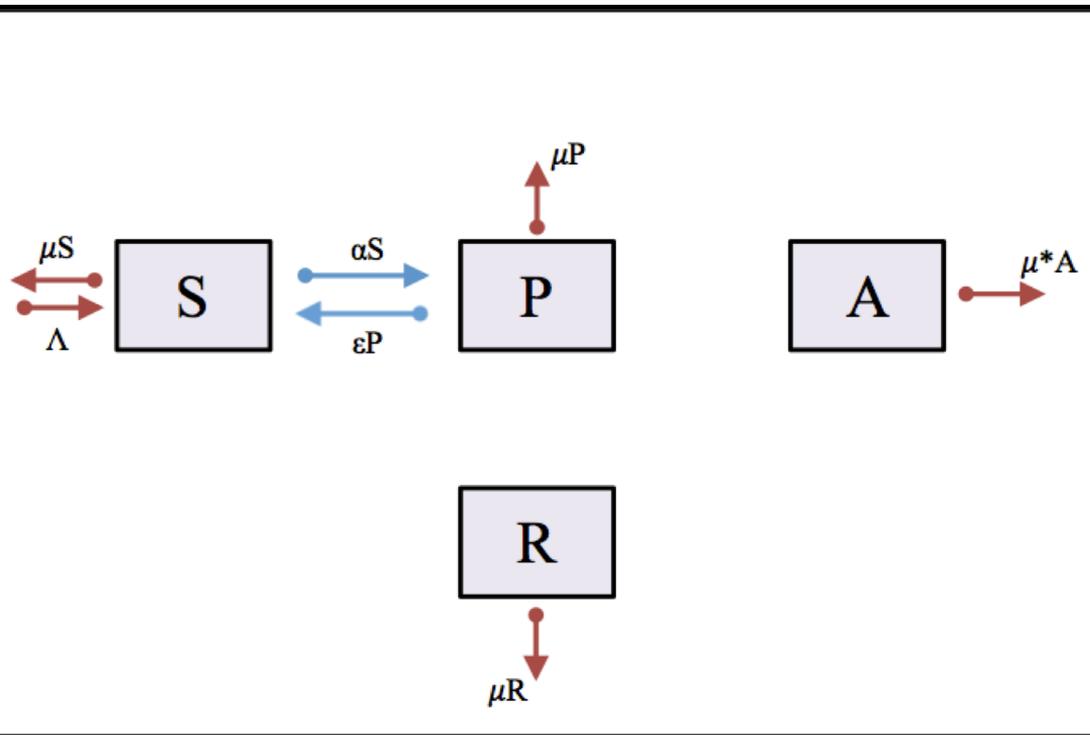
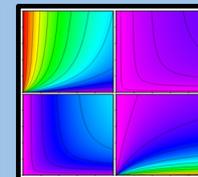
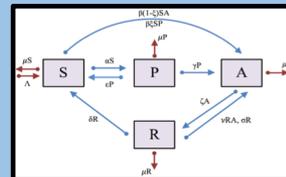
$\mu^* A$ — Enhanced Death Rate

Λ — Birth Rate

$$= \mu(S+P+R) + \mu^* A$$

- **S: Susceptible** – non-opioid users
- **P: Prescribed** – those with prescription opioids
- **A: Addicted** – those chronically abusing opioids
- **R: Rehabilitation** – those in rehab/treatment

Opioid Epidemic: Model



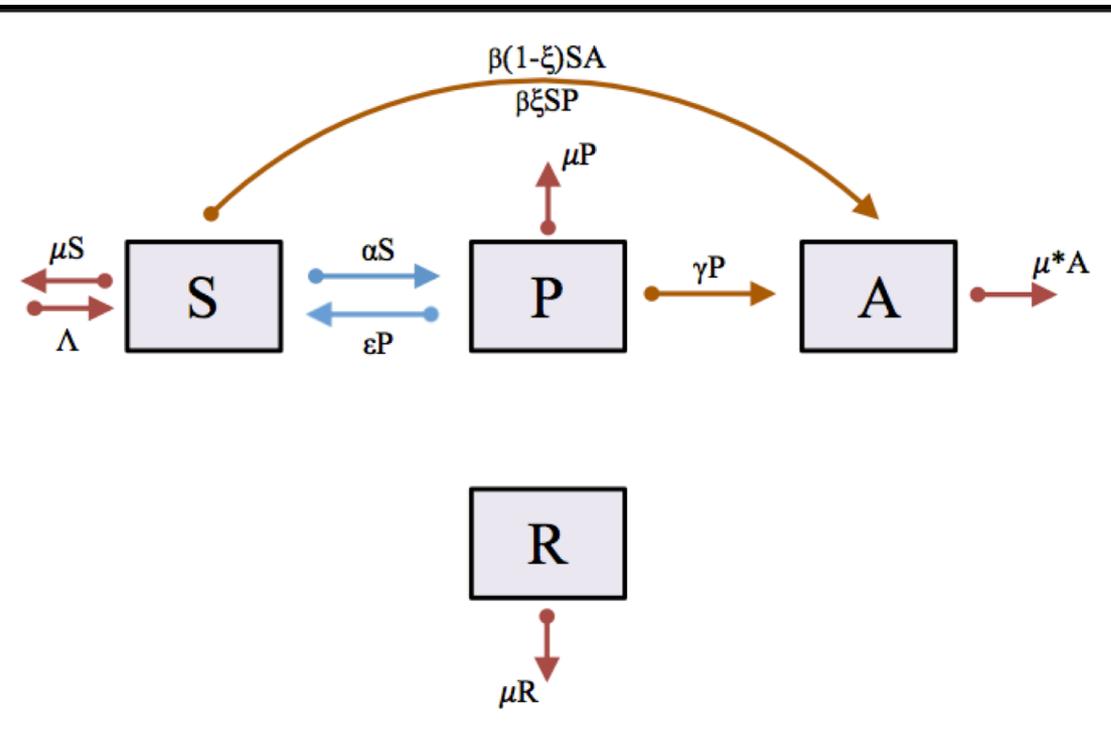
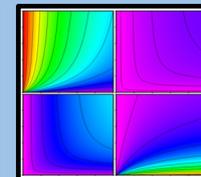
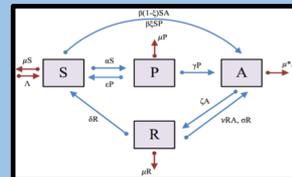
Dynamic: Prescribing Opioids

αS — Opioids medically prescribed

ϵP — Users that finish prescriptions and do not become addicted

- **S: Susceptible** – non-opioid users
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Opioid Epidemic: Model



Dynamic: Addiction Terms

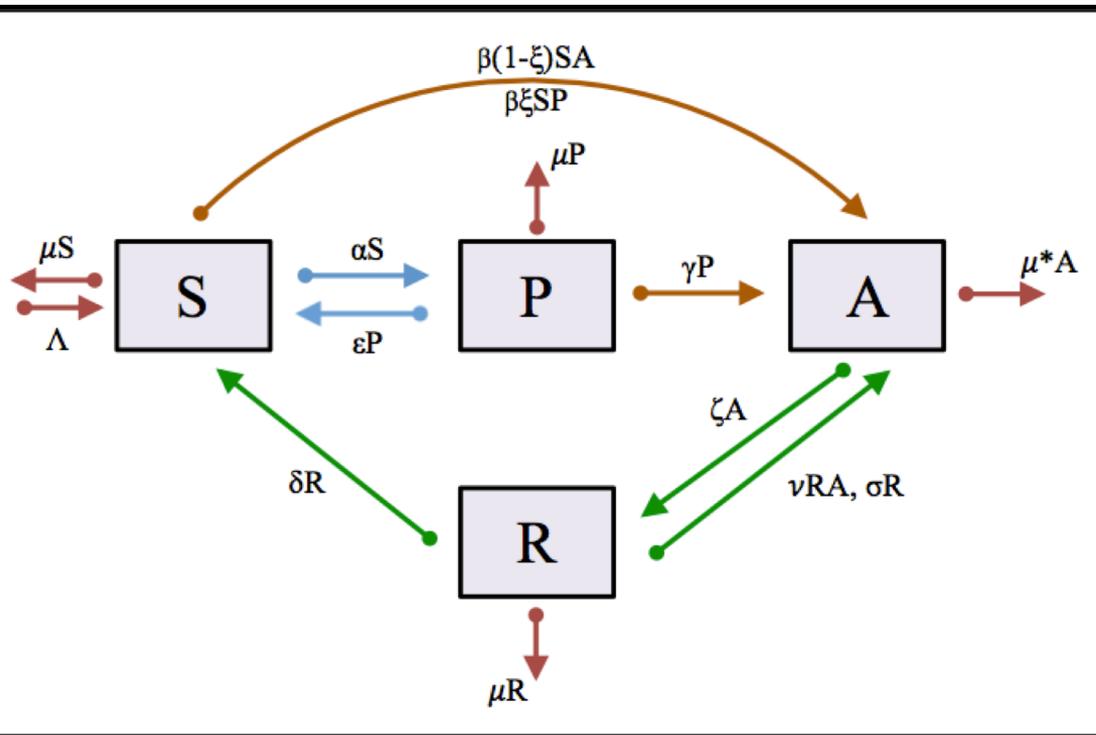
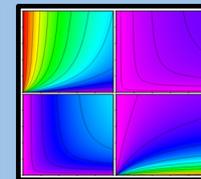
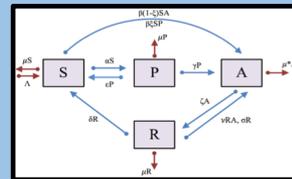
γP — Prescribed get addicted to their prescriptions

$\beta\xi SP$ — People get opioids from leftover prescriptions

$\beta(1-\xi)SA$ — People buying illegal opioids

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Opioid Epidemic: Model

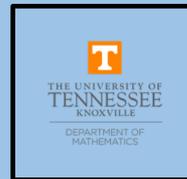
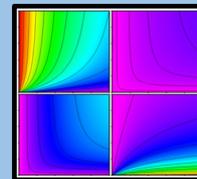
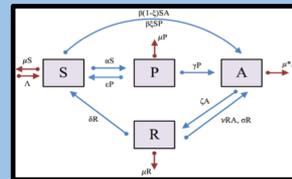


- **S**: *Susceptible* – non-opioid users
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Dynamic: Rehab/Relapse

- ζA — Addicts enter rehab/treatment
- δR — Addicts successfully complete rehab
- σR — Normal relapse
- νRA — Relapse due to addiction culture

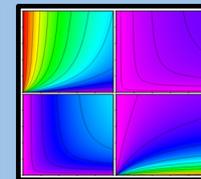
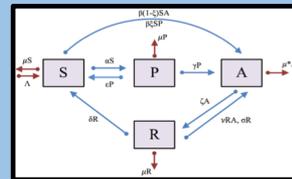
Opioid Epidemic: Model



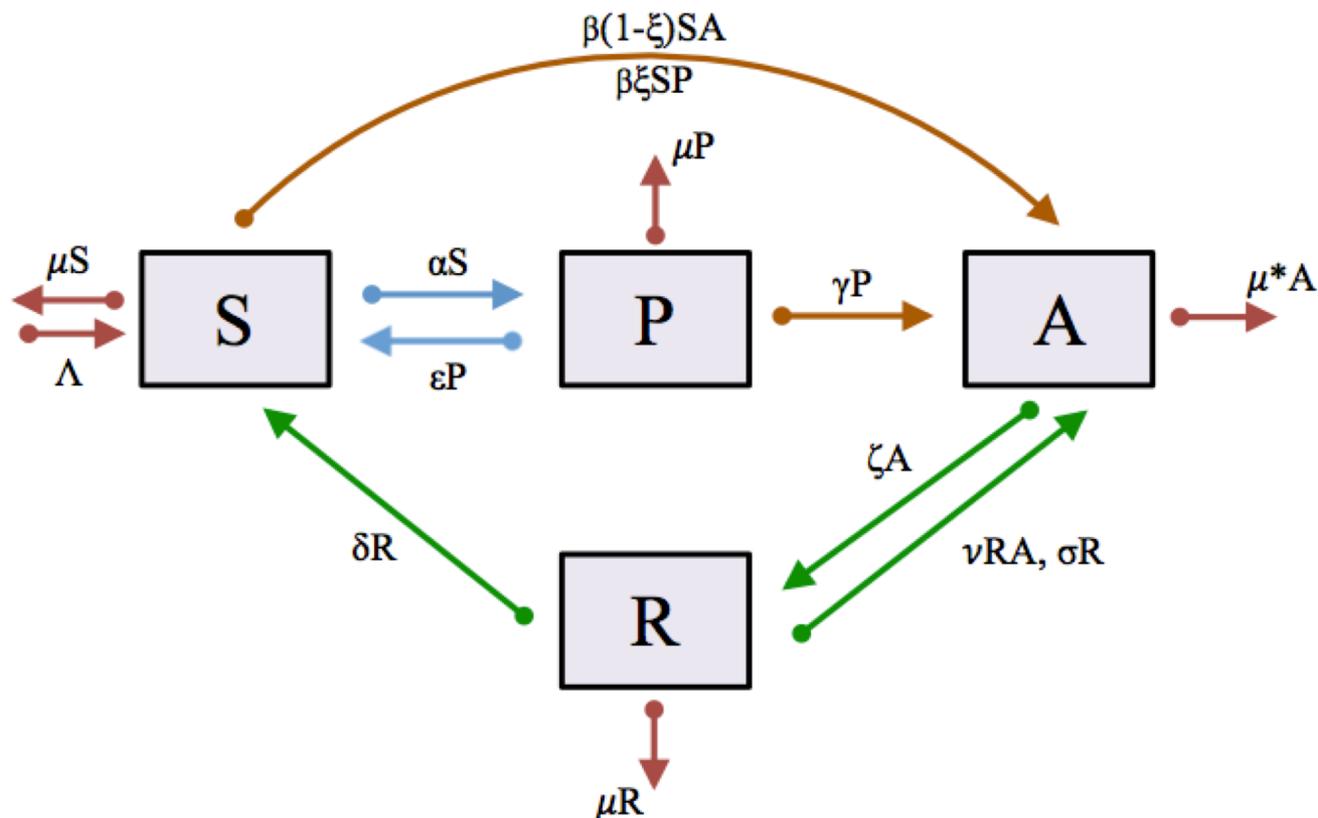
$$\begin{aligned}\dot{S} &= -\alpha S - \beta(1 - \xi)SA - \beta\xi SP + \epsilon P + \delta R + \mu(P + R) + \mu^* A \\ \dot{P} &= \alpha S - (\epsilon + \gamma + \mu)P \\ \dot{A} &= \gamma P + \sigma R + \beta(1 - \xi)SA + \beta\xi SP + \nu RA - (\zeta + \mu^*)A \\ \dot{R} &= \zeta A - \nu RA - (\delta + \sigma + \mu)R.\end{aligned}$$

- $S + P + A + R = 1$
- All parameters are positive
- $\mu^* \geq \mu > 0$

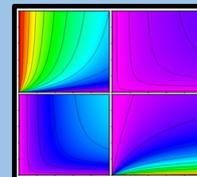
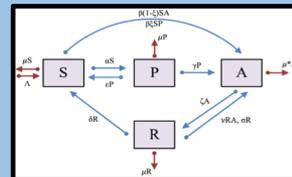
Opioid Epidemic: Model



First question: *Does our model predict that a totally addiction-free state is possible?*



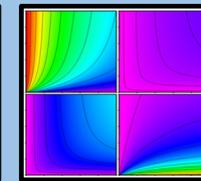
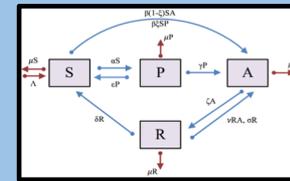
Opioid Epidemic: Model



First question: *Does our model predict that a totally addiction-free state is possible?*

Answer: *Sort of – stringent controls are necessary for existence of an addiction-free equilibrium.*

Addiction Free Society?



1st Requirement

$$\gamma = 0$$



Medically prescribed users do not get addicted to their prescriptions

2nd Requirement

OR

~~$$\beta = 0$$~~

~~No opioids left anywhere in model~~

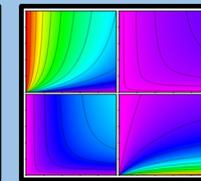
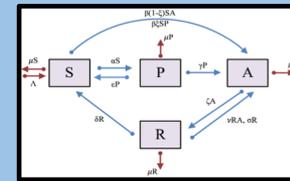
$$\xi = 0$$



Opioids only available through illicit means

(No secondary addictions due to prescriptions)

Addiction Free Society?



1st Requirement

$$\gamma = 0$$

Medically prescribed users do not get addicted to their prescriptions

2nd Requirement

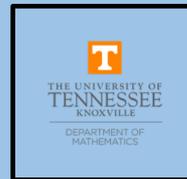
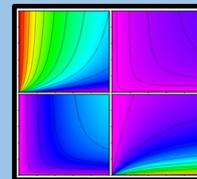
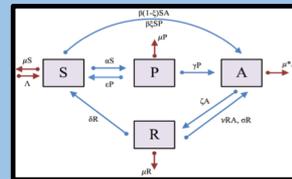
$$\xi = 0$$

Opioids only available through illicit means

What this tells us:

1. Stringent controls must be placed on how opioids are prescribed and administered
2. If this is achieved, the opioid model is converted to a more **traditional, illicit drug epidemic**

Addiction Free Society?



Given existence of a disease-free equilibrium....

$$S^* = \frac{\epsilon + \mu}{\alpha + \epsilon + \mu}$$

$$A^* = 0$$

$$P^* = \frac{\alpha}{\alpha + \epsilon + \mu}$$

$$R^* = 0$$

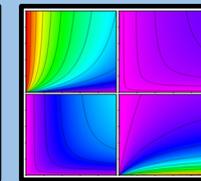
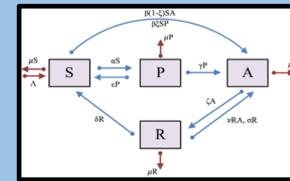
...we evaluate stability via R_0 , the basic reproduction number.

Methods used:

- Next generation matrix
- Jacobian analysis

(Details in Battista, Percy, and Strickland on ArXiv)

Addiction Free Society?



Result:

$$R_0 = \frac{\beta(\epsilon + \mu)}{(\alpha + \epsilon + \mu)(\mu^* + \zeta\Lambda)} = \frac{\beta S^*}{\mu^* + \zeta\Lambda}$$

secondary usage rate
↓
 βS^*

rehab rate
↑
 $\zeta\Lambda$

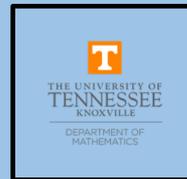
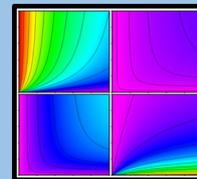
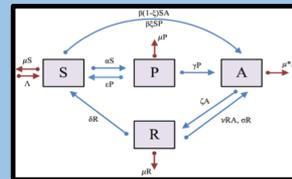
$$\Lambda = \frac{\delta + \mu}{\delta + \mu + \sigma}$$

rehab completion rate → ← relapse rate

Note: using estimated values of parameters from the literature, $R_0 < 1$...

So the opioid epidemic is not expected to be self-sustaining as an illicit-only epidemic!

Addiction Free Society?



Bifurcation analysis with respect to β when $R_0 = 1$:

Backward bifurcation occurs when:

$$\Lambda \Gamma \nu > (1 + \Gamma)(\mu^* + \zeta \Lambda)$$

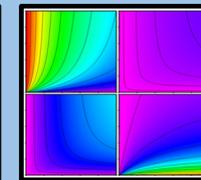
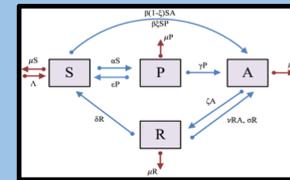
where:

$$\Gamma = \frac{\zeta}{\delta + \mu + \sigma}$$

$$\Lambda = \frac{\delta + \mu}{\delta + \mu + \sigma}$$

...but for expected realistic parameters, this is not expected to occur.

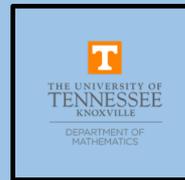
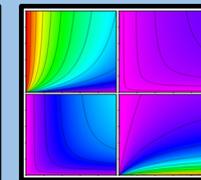
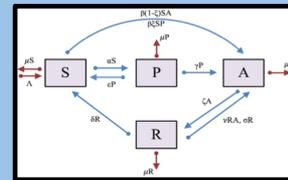
Parameter sensitivity



Sobol Sensitivity Analysis

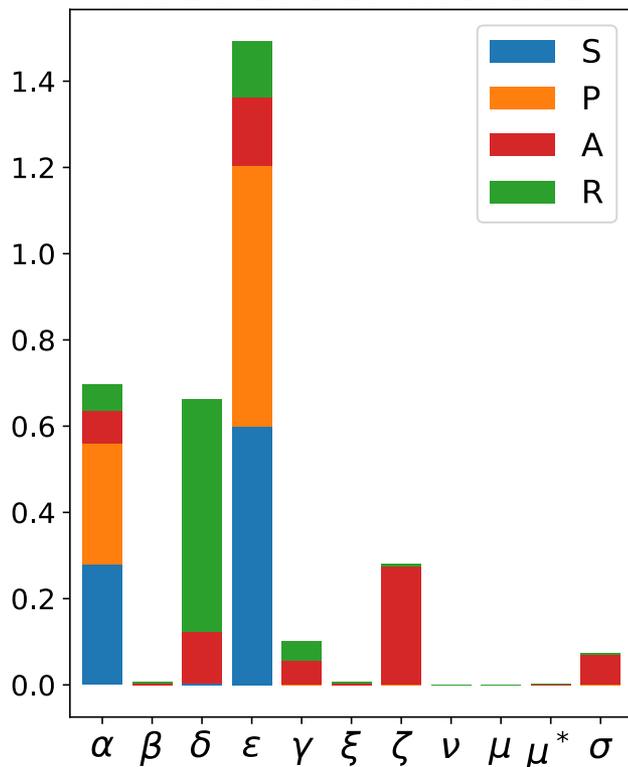
- Variance-based method
- Based on the ANOVA decomposition of the model's variance
- Concisely quantifies first-order and total-order effects (and anything between)
 - First-order: one-parameter changes at a time
 - Second-order: two-parameters changing at a time
 - ⋮
 - Total-order: effect of moving one parameter with any combination of others

Parameter sensitivity

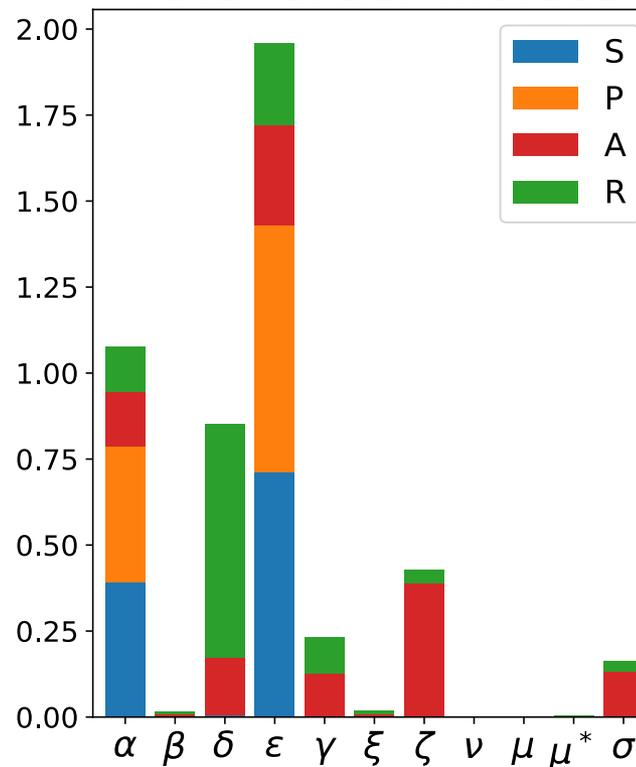


Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values of S,P,A & R

First-order indices

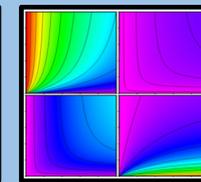
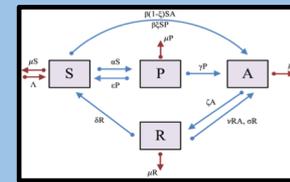


Total-order indices



	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

Parameter sensitivity

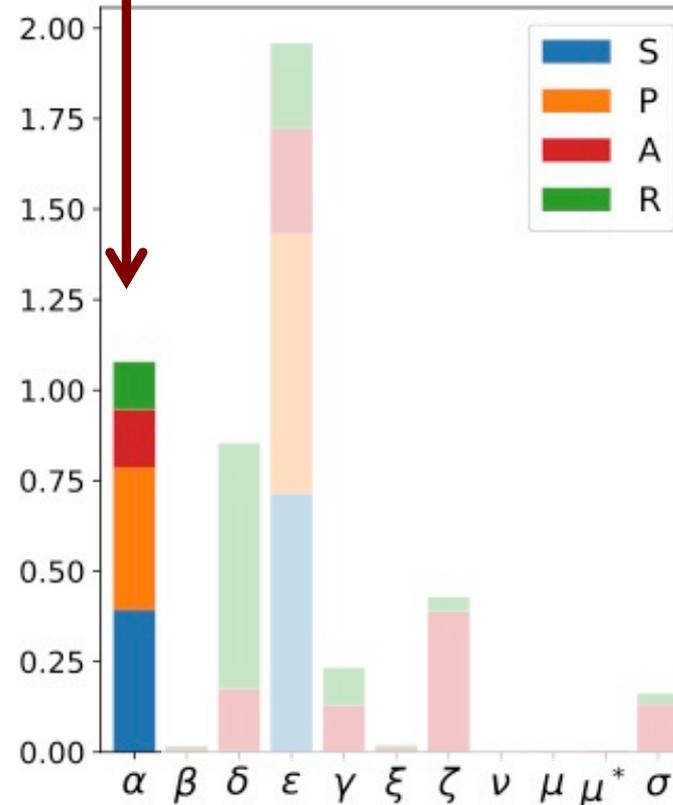


Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values.

Rate that opioids are prescribed

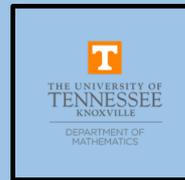
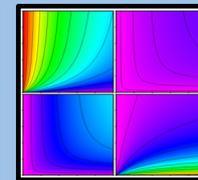
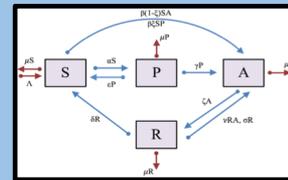
(α)

Total-order indices



	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

Parameter sensitivity

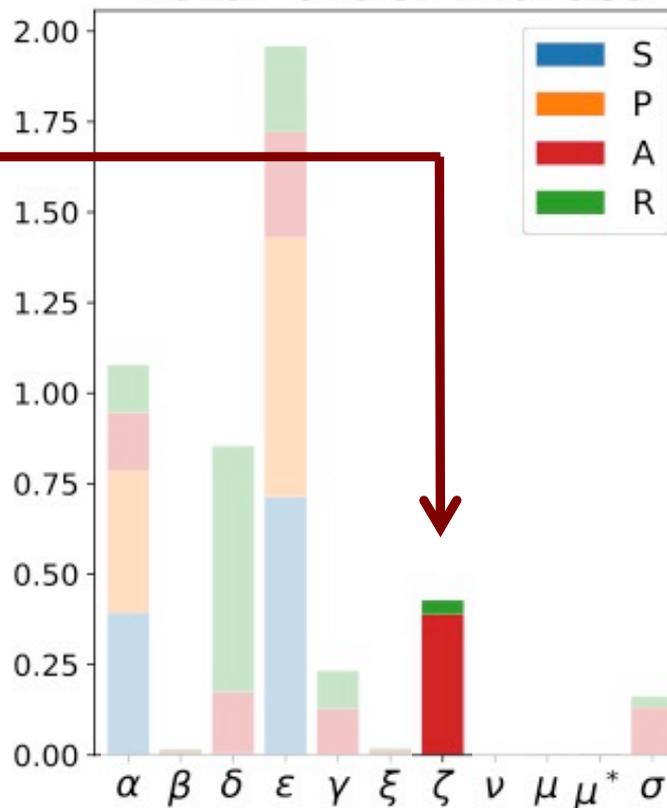


Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values.

Rate that opioids are prescribed (α)

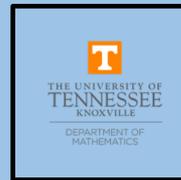
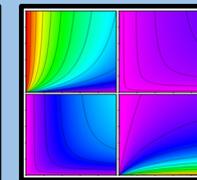
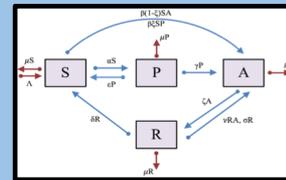
Rate addicts enter treatment (ζ)

Total-order indices



Parameter	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

Parameter sensitivity



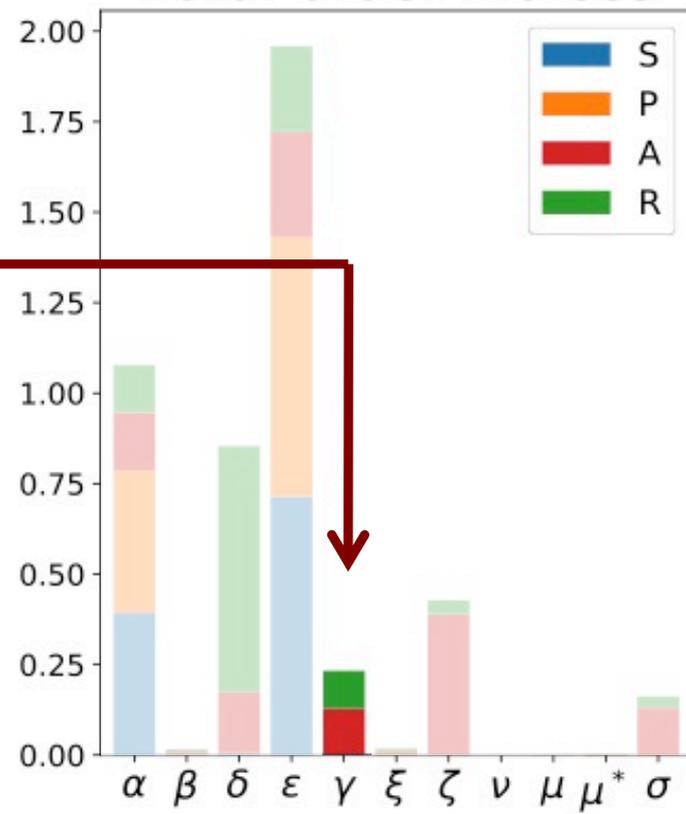
Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values.

Rate that opioids are prescribed (α)

Rate addicts enter treatment (ζ)

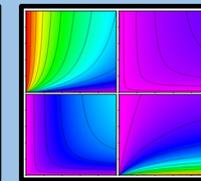
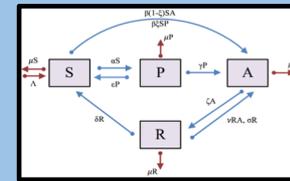
Rate prescribed users get addicted (γ)

Total-order indices



	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

Parameter sensitivity



Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values.

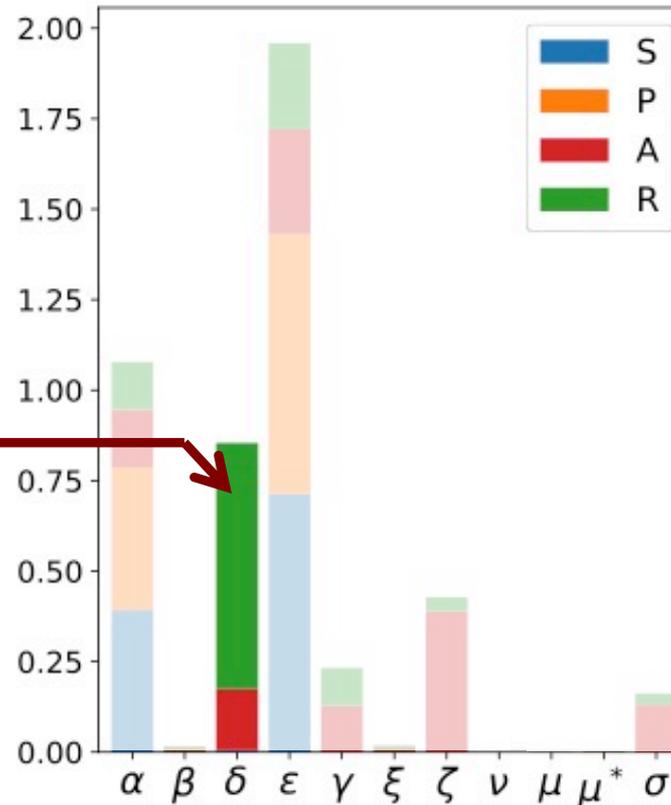
Rate that opioids are prescribed (α)

Rate addicts enter treatment (ζ)

Rate prescribed users get addicted (γ)

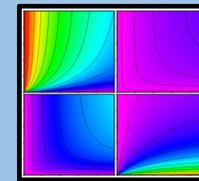
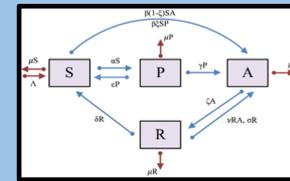
Rate of successful rehabilitation (δ)

Total-order indices



Parameter	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

Parameter sensitivity



Sobol Sensitivity: Taller bars correspond to more impactful parameter. Measured w.r.t. 10 yr. values.

Rate that opioids are prescribed (α)

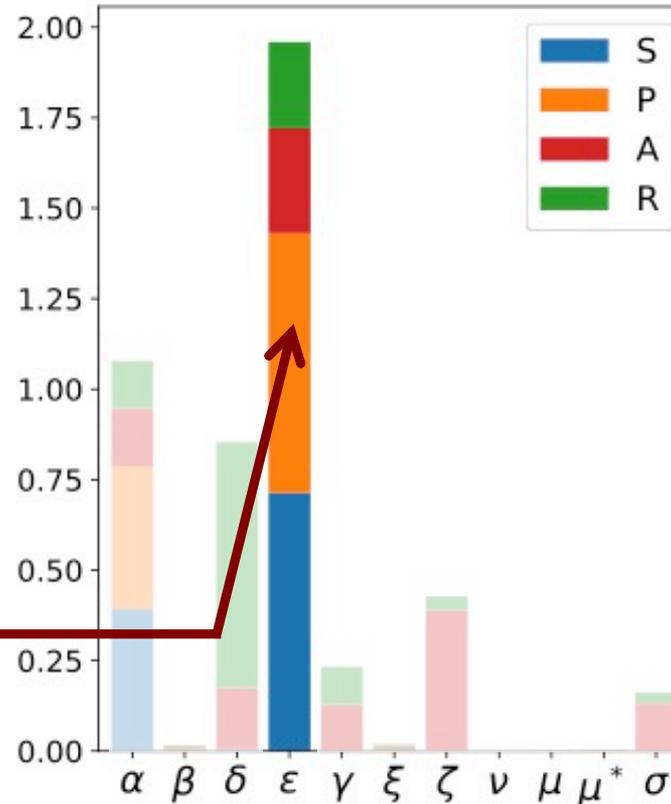
Rate addicts enter treatment (ζ)

Rate prescribed users get addicted (γ)

Rate of successful rehabilitation (δ)

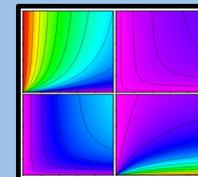
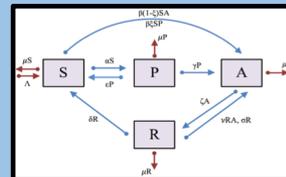
Rate of finishing prescription w/o addiction (ϵ)

Total-order indices

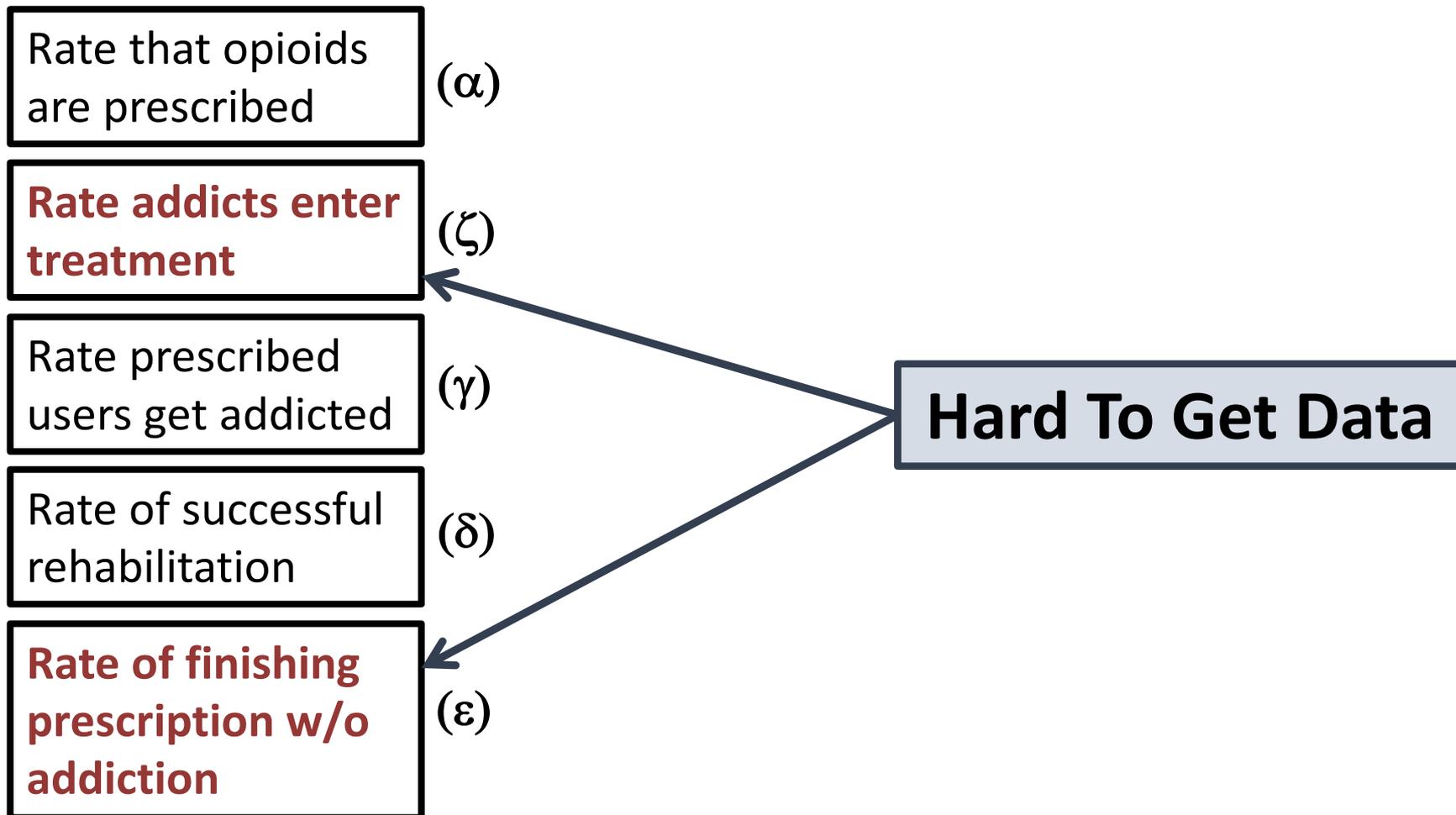


	Value Range
α	.02-.2
β	.00114-.0114
δ	0-1
ϵ	.8-8
γ	.00235-.0235
ξ	0-1
ζ	.2-2
ν	0-1
μ	.002305-.02305
μ^*	.003652-.03652
σ	0-1

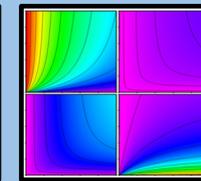
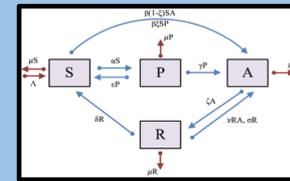
Opioid Epidemic: Data



Data connections: national, publicly available data



Opioid Epidemic: Data



Data connections: national, publicly available data

**Rate that opioids
are prescribed**

(α)

Rate addicts enter
treatment

(ζ)

**Rate prescribed
users get addicted**

(γ)

**Rate of successful
rehabilitation**

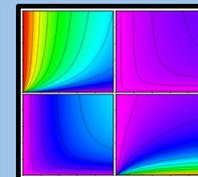
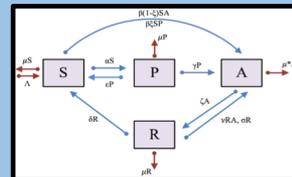
(δ)

Rate of finishing
prescription w/o
addiction

(ϵ)

**Some data: can
estimate these**

Opioid Epidemic: Data



Data connections: national, publicly available data

**Rate that opioids
are prescribed**

(α) 19.1/100 people prescribed per year (CDC '17) ,
but some will have ongoing prescriptions so
 $\alpha=0.15$ is a very rough estimate.

Rate addicts enter
treatment

(ζ)

**Rate prescribed
users get addicted**

(γ)

0.007 new addictions per prescribed user-year
based on comprehensive review (Vowels et al. '15)
and average usage times (Shah et al. '17)

**Rate of successful
rehabilitation**

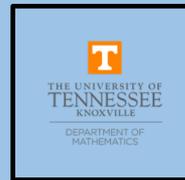
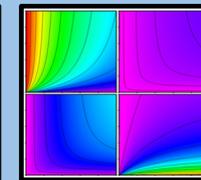
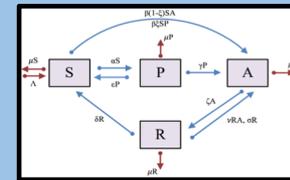
(δ)

10% treatment success rate (Weiss & Rao '17)

Rate of finishing
prescription w/o
addiction

(ϵ)

Basic comparisons to data



Validation Step

Rate that opioids are prescribed (α)

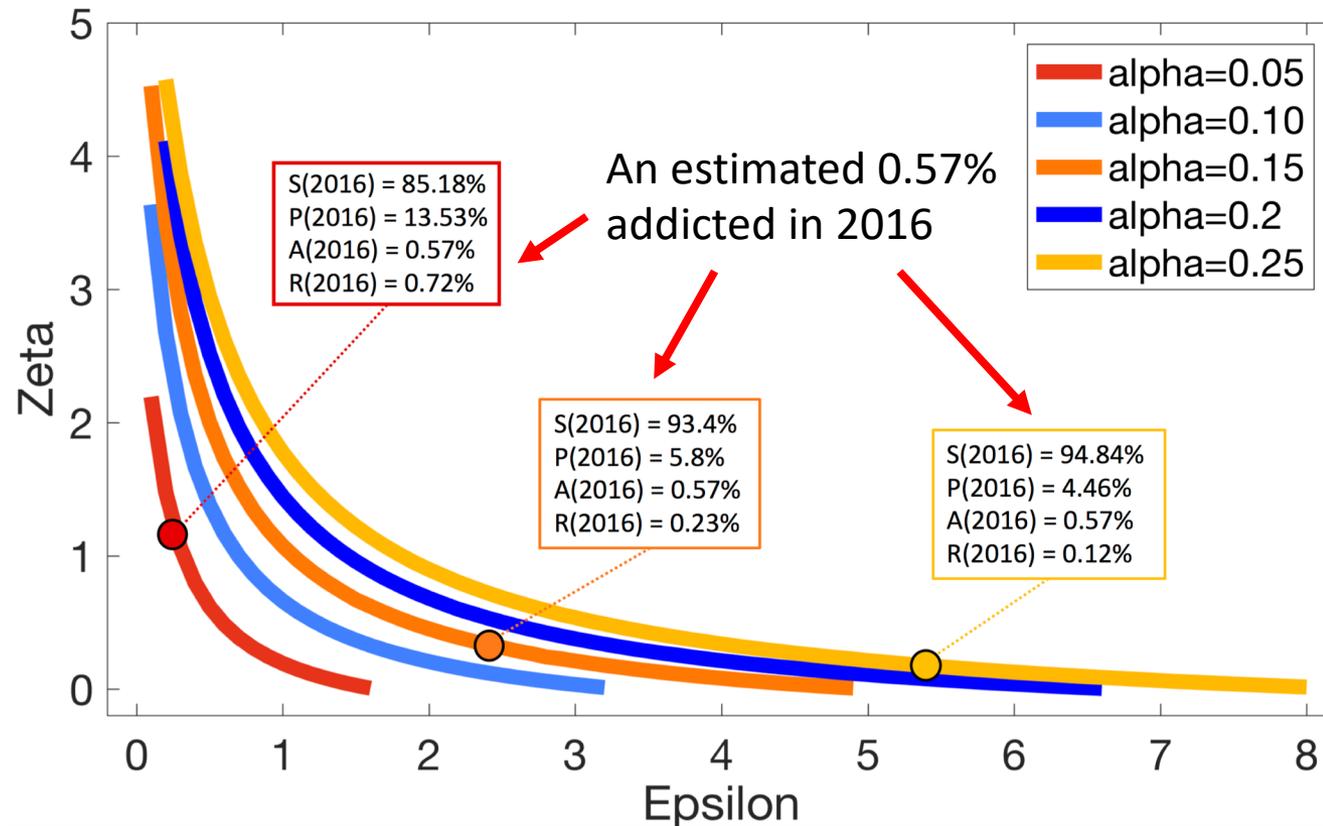
Rate addicts enter treatment (ζ)

Rate prescribed users get addicted

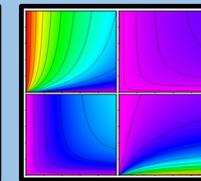
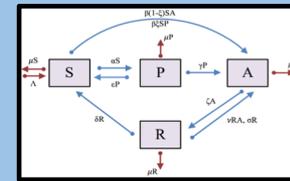
Rate of successful rehabilitation

Rate of finishing prescription w/o addiction (ϵ)

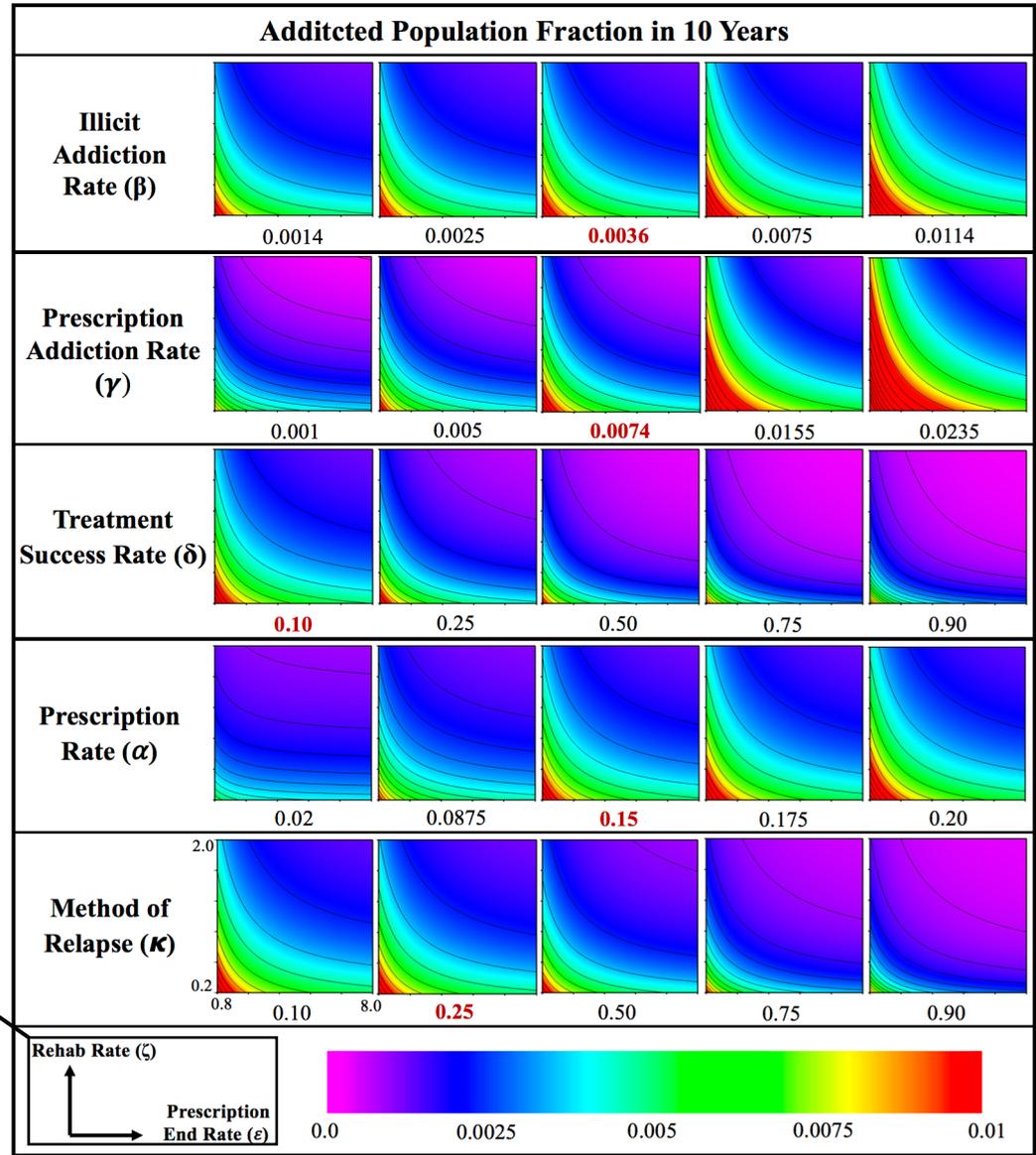
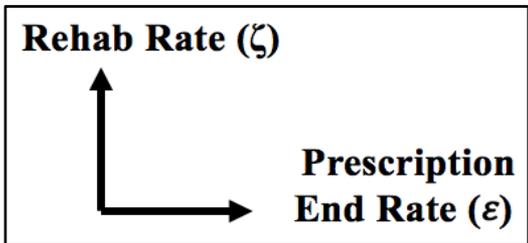
Combinations of α , ζ and ϵ resulting in 2016 deaths



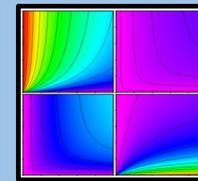
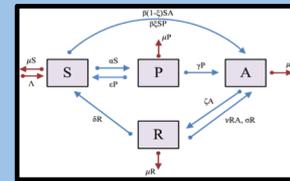
Parameter analysis



Numerical parameter space exploration for addicted population fraction after 10 yrs.



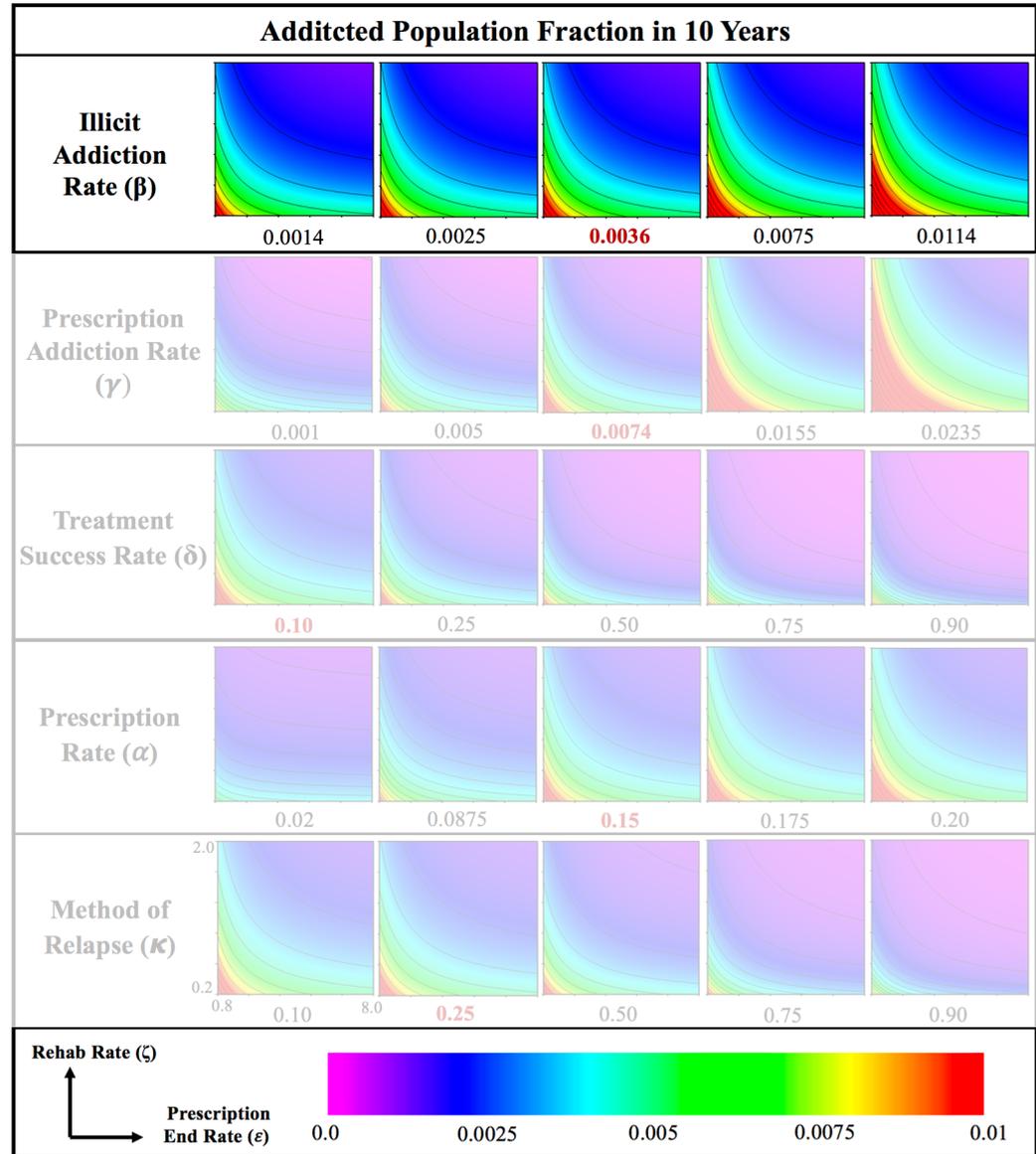
Parameter analysis



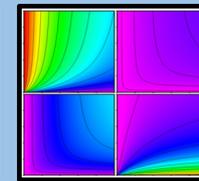
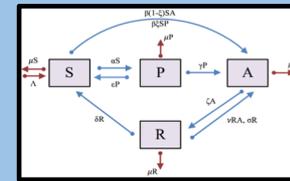
Increasing Illicit-based Addiction Rate

Takeaway:

An increase in illicit opioids can increase the amount of rehab + prescription control needed. Decreasing illicit opioids has little effect.



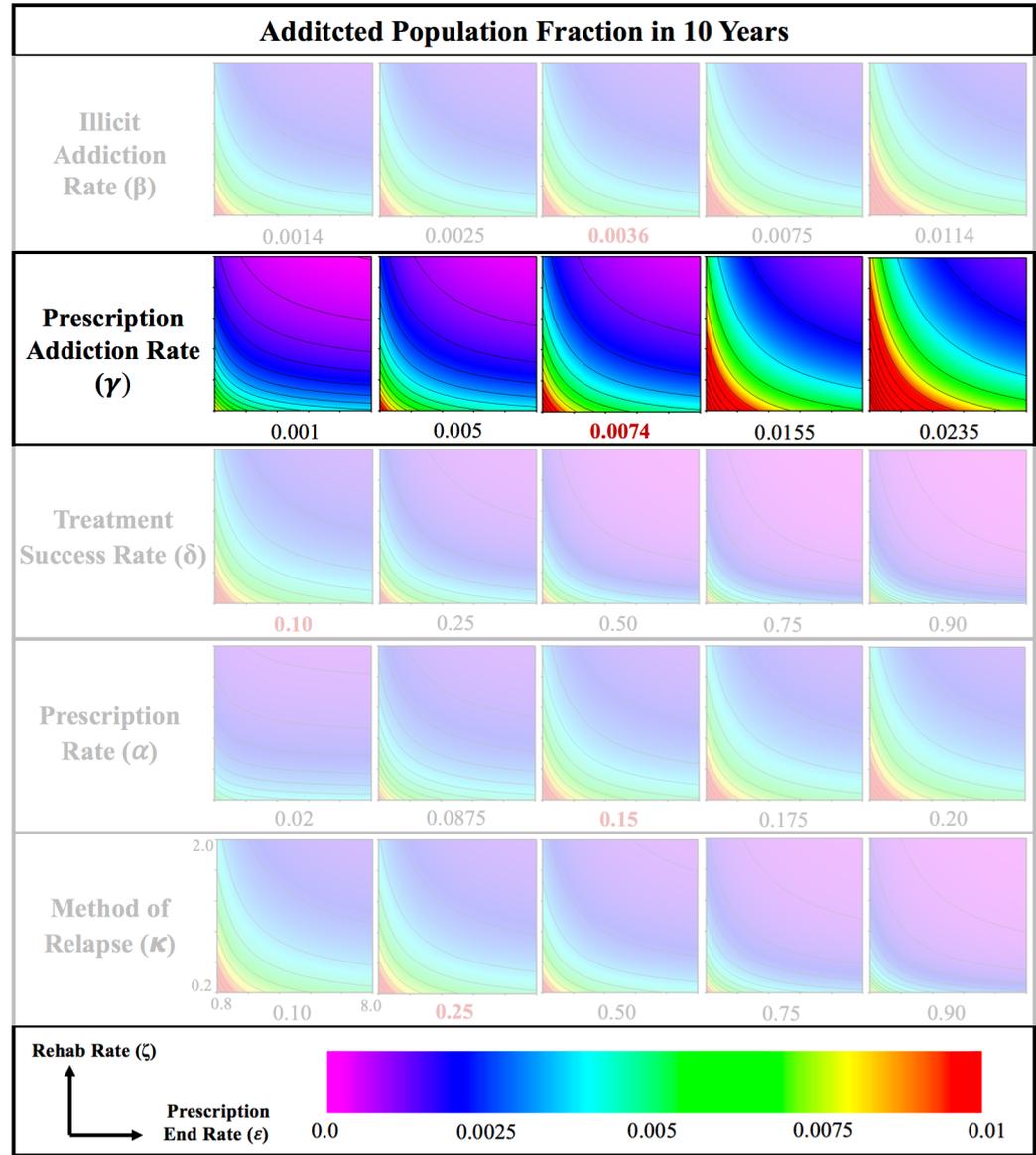
Parameter analysis



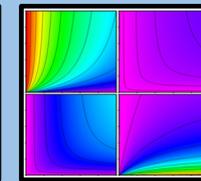
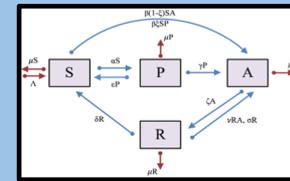
**Varying rate
prescription users
get addicted**

Takeaway:

*Drastic change both in
number of addicted
and effectiveness of
treatment.*



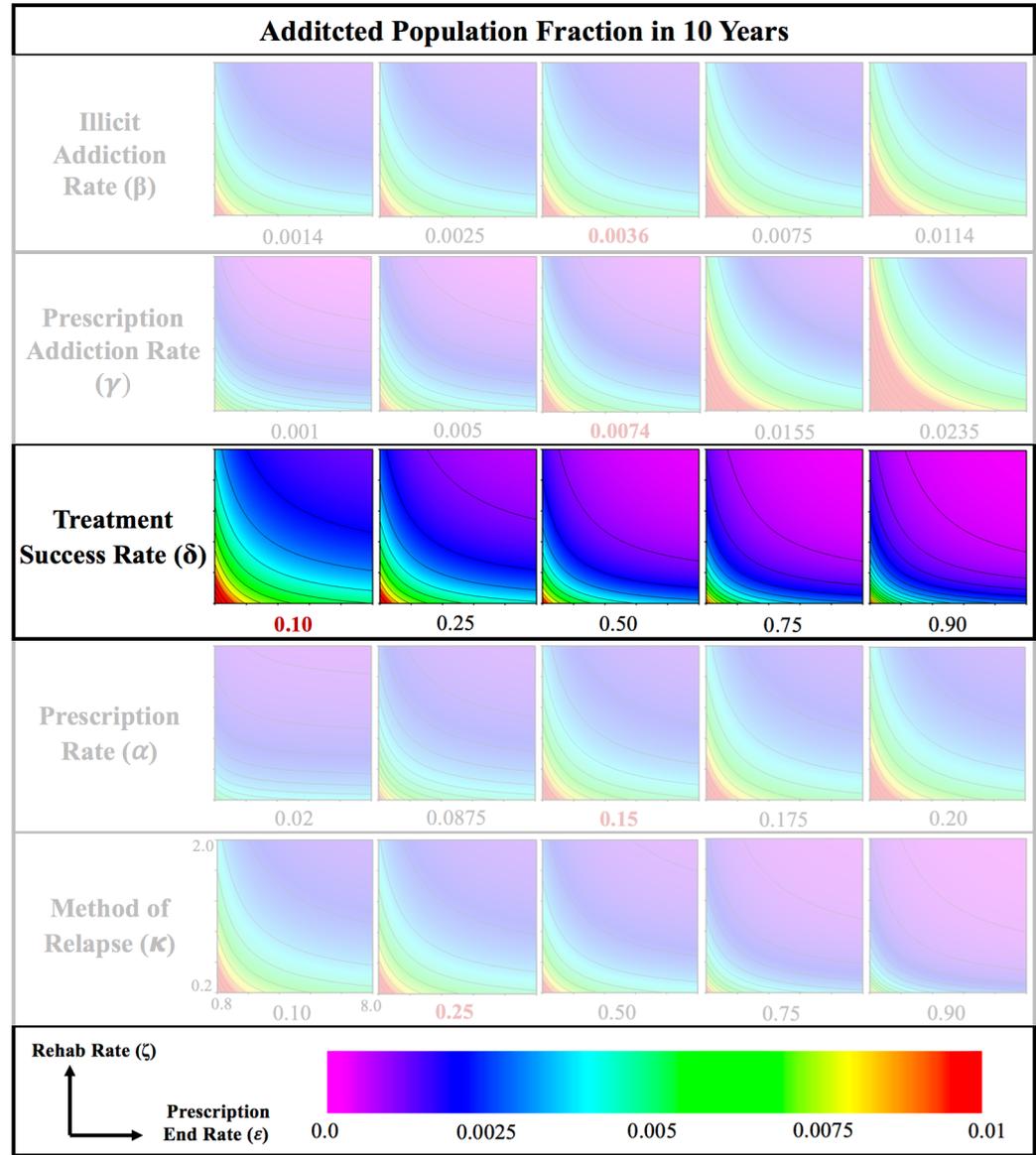
Parameter analysis



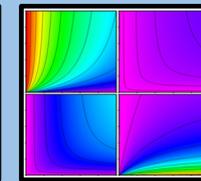
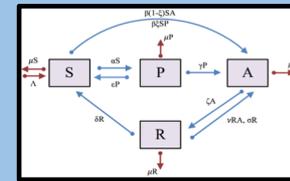
Increasing rate of successful rehab

Takeaway:

More successful treatment = more drastic effect of getting people into treatment, particularly when the rate of starting treatment is low



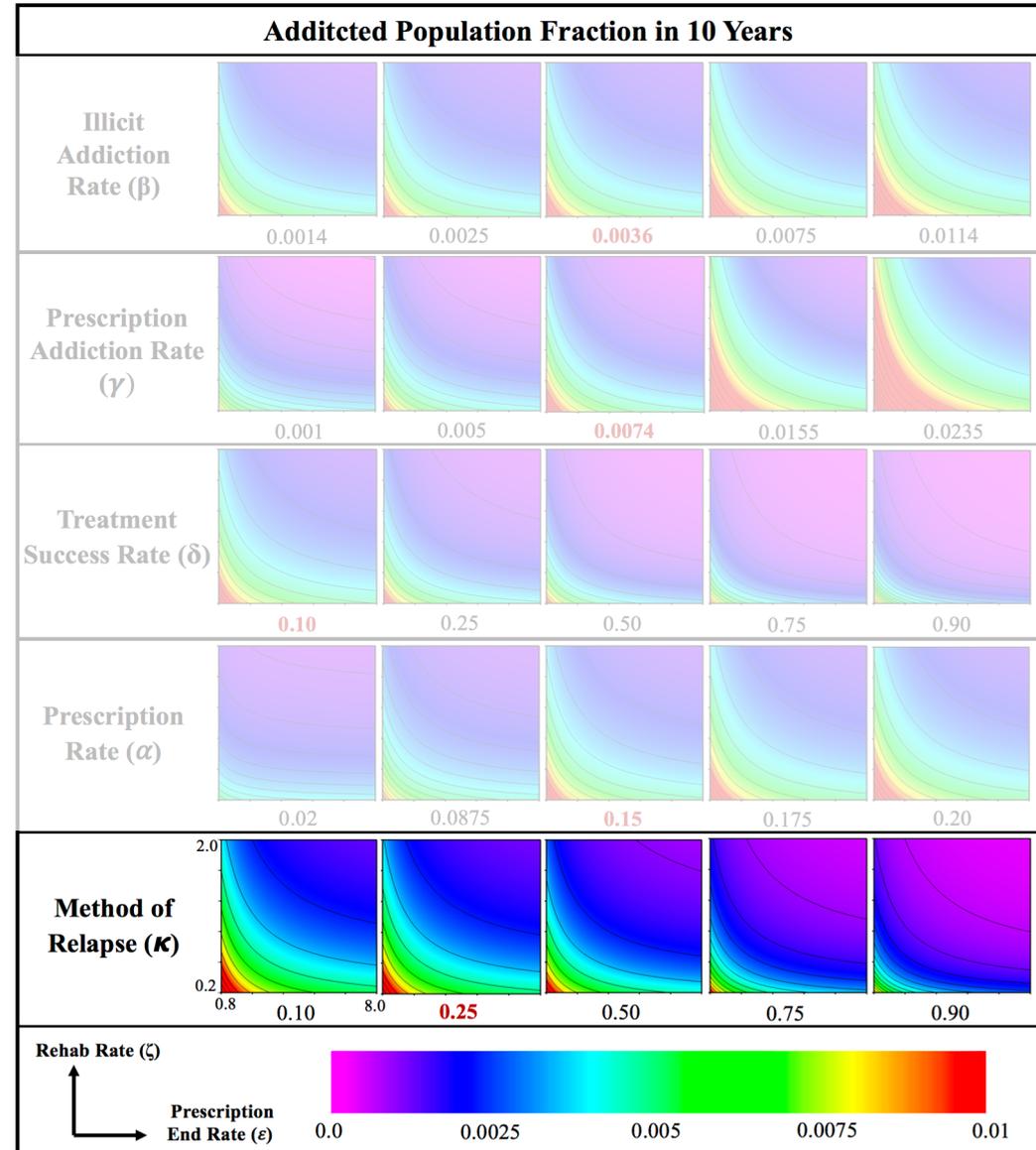
Parameter analysis



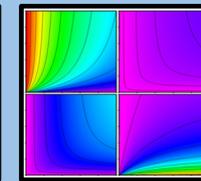
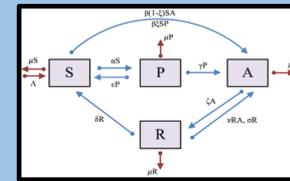
How addicts relapse

Takeaway:

Model is not sensitive to small changes, but if intrinsic relapse rate can be made low compared to illicit-based relapse, other controls are more effective



Parameter analysis

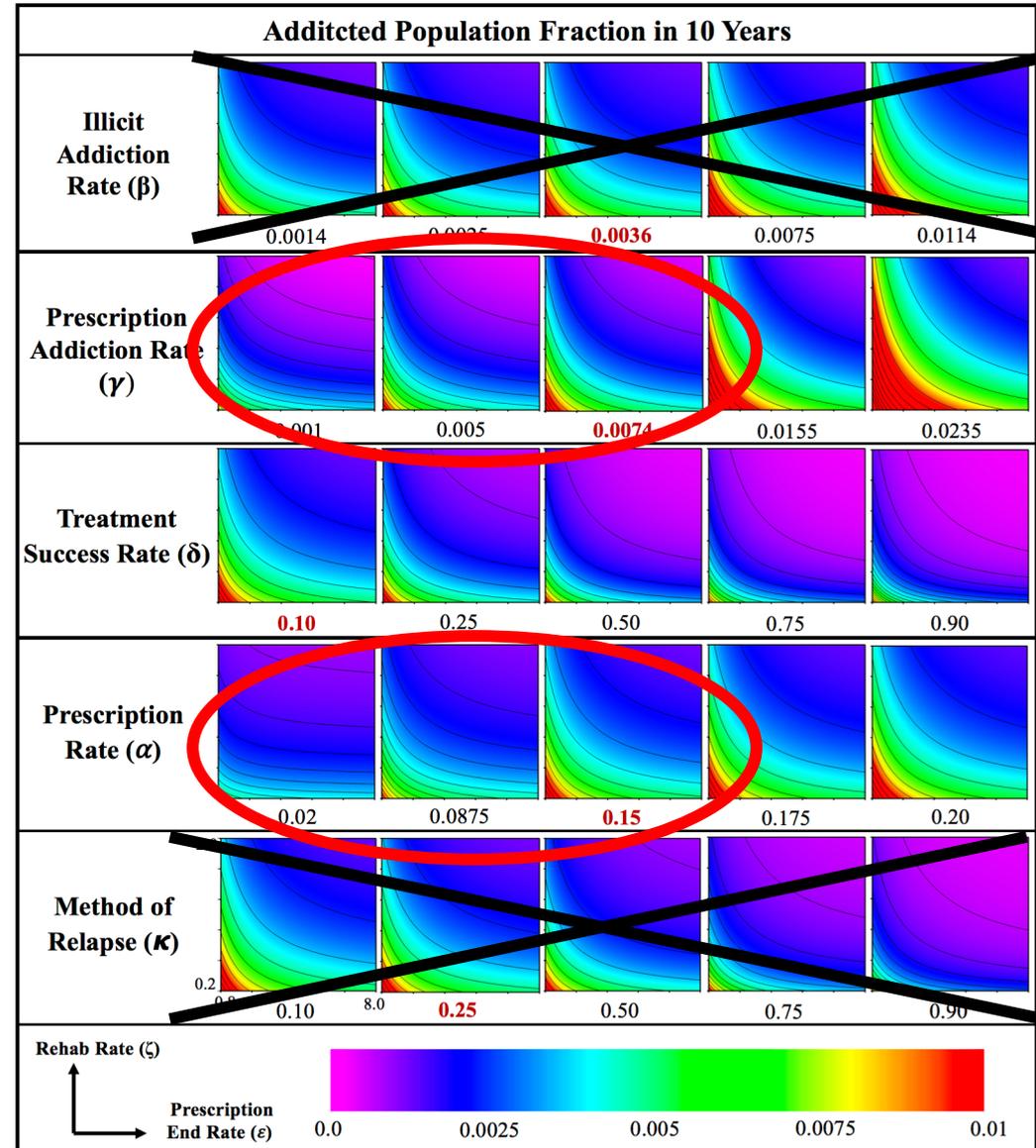


Summary

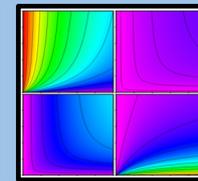
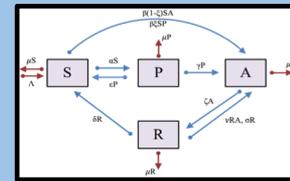
Decrease prescription-induced addictions by managing risk and prescribing less.

Then....

Increase the treatment entry rate (and treatment success rate).



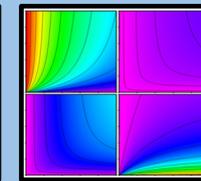
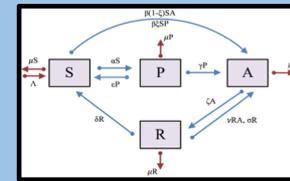
Summary



Model Summary:

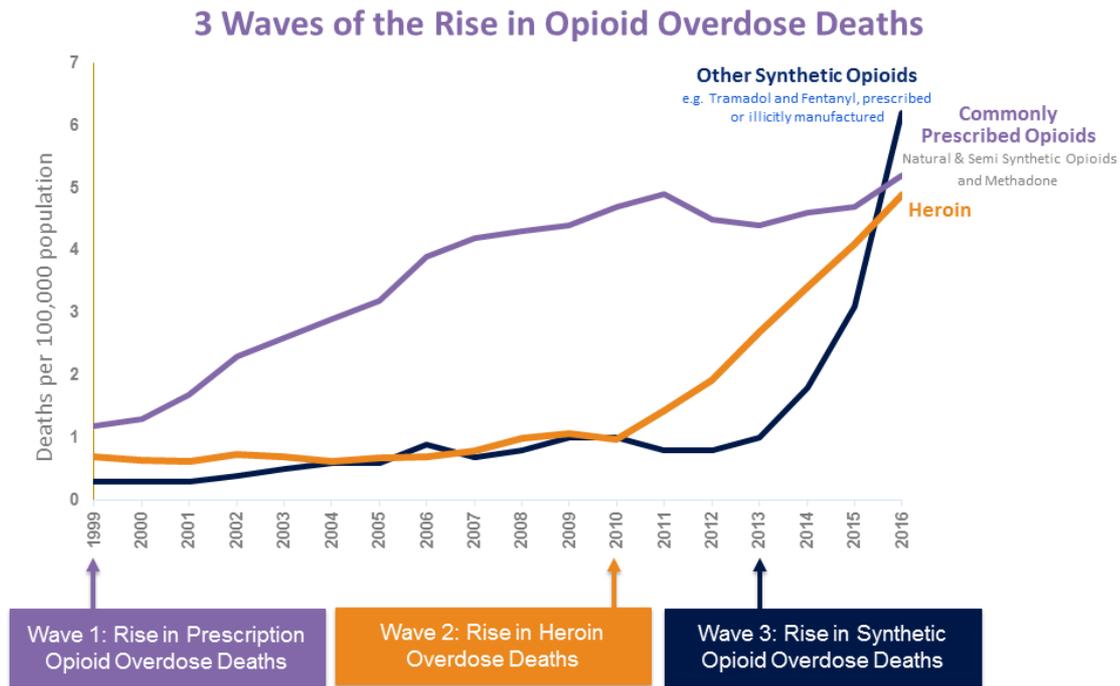
- *Complete elimination of opiate addiction is not possible w/o stringent controls on medication*
- *Controlling patients' prescription-induced addiction should be prioritized over other addiction sources: manage prescription start (α), finish (ε), and risk (γ)*
- *Rehab efforts can then make a profound impact, even if per-case treatment success rate is still somewhat low*
- *This is a first model that can certainly be improved upon and explored further!*

Summary



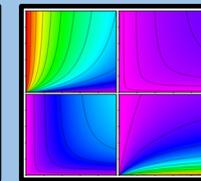
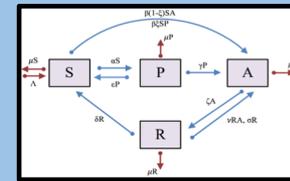
Current and Future Work with Suzanne Lenhart and Tricia Phillips

- Add heroin/fentanyl to model, revisit assumptions



SOURCE: National Vital Statistics System Mortality File.

Summary

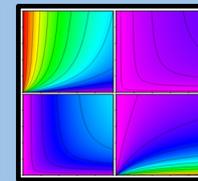
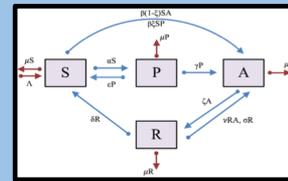


Current and Future Work

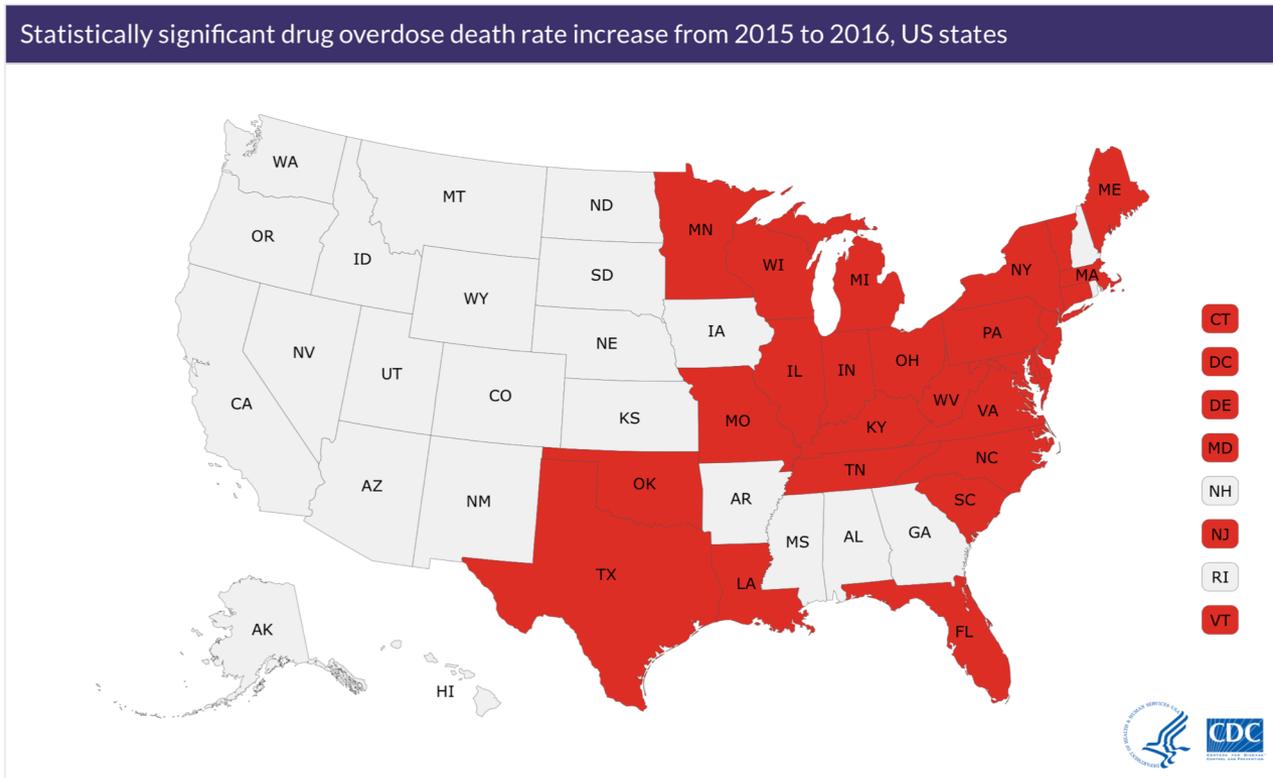
with Suzanne Lenhart and Tricia Phillips

- *Add heroin/fentanyl to model, revisit assumptions*
- *Use state-level data instead of national, try to get better parameter estimates and time-series data*
- *Age/sex/usage level stratification*
- *Bayesian parameter fitting and uncertainty analysis*
- *Study control strategies to determine best management solutions given limited resources*

Summary



Because the problem is only getting worse...



Statistically significant increase

Statistically significant increase from 2015 to 2016

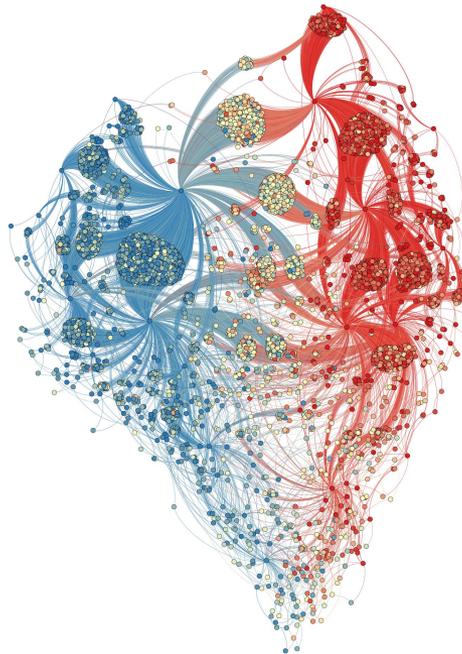
- No
- Yes

Questions?

cstric12@utk.edu

www.ChristopherStrickland.info

Battista, Percy, Strickland, *Modeling the Opioid Epidemic*, Submitted.
Preprint on ArXiv!



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