Proceedings of the 2017 Winter Simulation Conference
W. K. V. Chan, A. D'Ambrogio, G. Zacharewicz, N. Mustafee, G. Wainer, and E. Page, eds.

MODELING APPROACHES, CHALLENGES, AND PRELIMINARY RESULTS FOR THE OPIOID AND HEROIN CO-EPIDEMIC CRISIS

James Benneyan
Jacqueline Garrahan
Iulian Ilieş
Xiaoli Duan

Healthcare Systems Engineering Institute
Northeastern University
177 Huntington Avenue, 12th Floor
Boston, MA 02115, USA

ABSTRACT

The U.S. is in the grips of a devastating opioid and heroin co-epidemic affecting nearly all socio-economic populations at great human (~7,800 new users/day) and financial ($78.5 billion/year) costs but with no obvious solution. We describe recent work and challenges to develop, integrate, and use several analytic multi-scale simulation models of these epidemics to develop insight into the epidemic's complex underlying dynamics, generate causal hypotheses, and inform effective policy interventions. We developed preliminary agent-based, differential equation, network spread, and cellular automata models that reasonably replicate at multiple scales the past 17 years of this epidemic's growth and spread at town, county, state, and national levels. Results suggest that some current approaches are unlikely to be very effective, some in fact may worsen the epidemic, and ultimately only certain combinations and sequences of policies are likely to have value, with important implications on both model architecture and policy optimization.

1 INTRODUCTION

The massive influx of prescription opioids and heroin into American communities and their heartbreaking societal impact is increasingly alarming to legislators, medical practitioners, and the general public, with near daily headlines and a recent report from the U.S. Surgeon General calling for immediate action (Office of the Surgeon General 2016). The interdependent opioid and heroin crises (and now fentanyl) gripping the United States are impacting all aspects of society at crippling social and financial cost, but with causal dynamics and effective interventions, strategies, and policies being largely unclear. Opioid-related overdoses have more than quadrupled since 1999, reaching a staggering 33,000 deaths in 2015 (~90 per day) with roughly 15,000 due to prescription opioids, 13,000 to heroin, and 5,000 to emerging more dangerous synthetic substitutes (e.g. fentanyl and its derivatives) as abusers transition over time to increasingly more powerful drugs (National Center for Health Statistics 2016). The estimated economic burden of this crisis exceeds $78.5 billion/annually (Center for Disease Control and Prevention 2013, Florence et al. 2013) with abuse and overdose rates continuing to rise and no indication of abating (Figure 1); in March 2017, the governor of Maryland declared a statewide state of emergency and issued standing prescriptions for every citizen of Baltimore for the naloxone (Narcan) overdose antidote (The State of Maryland 2017).

Effective interventions, however, are unknown due to the rate at which these epidemics have emerged, dynamics by which abuse begins and spreads across regions and social networks, and inter-relationships between each drug abuse type, substance availability, drug switching, and market forces – often leading to sub-optimal and even harmful interventions. For example, although many advocacy groups recommend

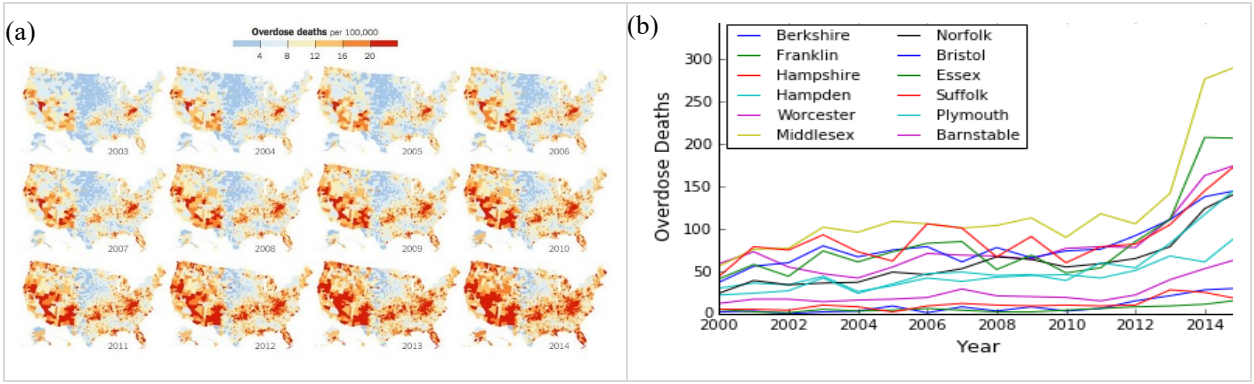

Figure 1: Spread of opioid and heroin epidemics, 2000-2015. Overdose deaths by (a) state and (b) Massachusetts county, showing geographic trends and dramatic increases since 2010 (sources: CDC, MA DPH).

reduced opioid prescribing to address the problem at its source, other policy experts (and recent data) suggest that efforts to limit supply in some cases may drive more users to cheaper and more easily available heroin, for which death rates are higher; relative street costs of opioids and heroin are roughly $100/gram versus $10/bag, with the latter being much more readily accessible. Law enforcement activities to restrict heroin supply also often result in huge amounts of fentanyl (easily produced in household kitchens, much of it tainted) flooding the market and resulting in mortality spikes of potentially more people than saved.

One thing that is clear, however, is that current approaches are not working and in some cases may be exacerbating the crisis. Legislative reform, increased prescribing regulation, and state-to-state sharing of prescription monitoring databases also may cause as much harm as good, e.g. with some addicts switching to more dangerous cheaper drugs to avoid detection. Broader naloxone availability also may encourage addicts to practice riskier drug behaviors, while even less is known about the effectiveness of patient-level interventions (methadone maintenance therapy, treatment agreements, urine testing) (Seal et al. 2003, Brennan et al. 2016, Haegerich et al. 2014). The 2016 Surgeon General's report thus recommended immediate multi-faceted action including efforts to better understand both effectiveness and negative impacts of various response strategies, an ideal area for operations research modeling. We report on preliminary work to develop spatial-temporal models of these epidemics to help understand mechanisms by which drug abuse propagates within and between communities, analyze proposed interventions and unintended consequences, and develop explanatory models of historical patterns to help design more effective prevention strategies (Figure 2). Since a combination of interventions likely will be most effective and given the span of contributing dynamics (pain management attitudes, pharmaceutical proliferation, prescribing practices, illicit markets, etc), we have engaged individuals from all problem perspectives early in our model-building process

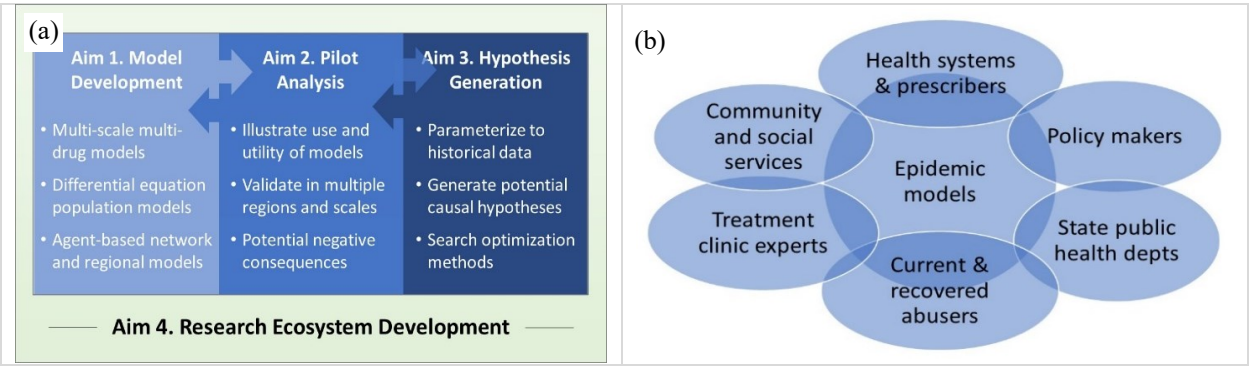

Figure 2: (a) Overall long-term research aims to develop validated models, conduct policy analysis, and generate causal hypotheses and insights; (b) Interdisciplinary multi-stakeholder research advisory consisting of policy makers, state public health departments, addiction treatment, and social workers.

with all models also informed via ongoing feedback from an advisory group of policy makers, state public health departments, addiction treatment, and social workers serving multiple populations.

2 MODELING APPROACHES

2.1 Model Development and Challenges

Three types of epidemic models were developed and validated iteratively, extending concepts used in similar infectious disease, migration, and diffusion problems (Halasa et al. 2013, Mishra et al. 2014). Aside from a few stylized examples, little model-based research exists in the literature on this critical problem (Hoffer, Bobashev, and Morris 2009). Our work therefore has focused on establishing analytic frameworks and pilot results for differential equation, cellular automata, and network diffusion models (deterministic and stochastic), building on the respective strengths of each to capture (i) *population-level* interdependent dynamics, (ii) *geographic-level* topology spread, and (iii) *individual-level* influence across networks. For example, our differential equation model extends 'susceptible-infected-recovered' (SIR) epidemic ideas and includes single-region/single-drug and multi-region/multi-drug cases, where time periods and regions can represent multiple scales (weeks, months, years; towns, counties, states). Cellular automata constructs typically are useful to represent regional spread and evolution, and network diffusion constructs can help capture social influences, person-to-person spread, and within-population topologies (Pfeifer et al. 2008). A central idea of all models, separately and combined, is to capture the complex epidemic dynamics over time, between drugs, over different types of geographic topologies and scales, and based on different types of social networks within and across these communities (Figure 3). All models were developed in MATLAB and Python with an eye on their eventual combination into an integrated model.

Building on these basic foundations, technical aspects and challenges beyond traditional disease spread models include addressing heterogeneity, addiction progression, drug switching, market dynamics, supply and demand pricing, cumulative exposure to abusing individuals (including consequence awareness as dynamic functions of mortality rates), and person-to-person network influencers. Heterogeneous modeling considerations include multiple susceptible populations (naive, prescription users, chronic abusers), spread transmission modes (peer influence, drug availability, dependence history, regional migration), and drug classes (varying uptake, abuse duration, mortality rates). To address parameter estimation challenges, we are combining expert input with statistical fitting to state mortality data to maximize model-vs-empirical

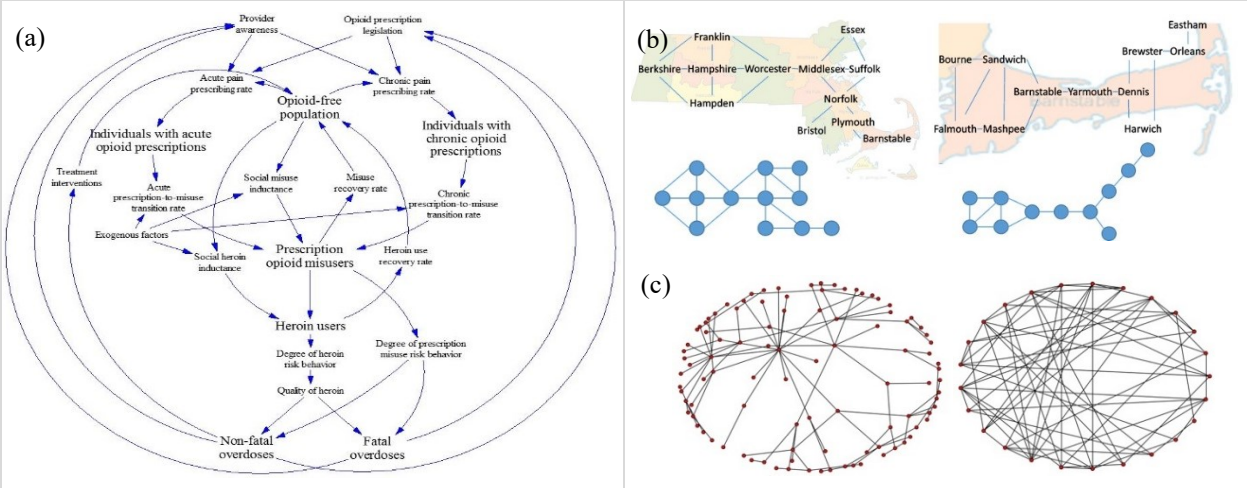

Figure 3: General epidemic dynamics: (a) Single-drug single-region causal loop diagram, (b) Examples of regional topologies (MA counties, Cape Cod towns), (c) Typical individual-level networks (Erdős-Rényi, Barabási-Albert).

agreement (minimum mean squared error, absolute percentage error, etc.), as well as input sensitivity analysis. This also is involving experimentation with various search algorithms (e.g. evolutionary, swarm, tunneling, annealing). Model validation and refinement has included logic and assumption reviews with subject matter expert stakeholders, scenario testing across multiple settings, and directional verification.

2.2 Dynamical Systems Models

A common 'top-down' approach to modeling epidemics is via coupled dynamical equations such as in classic SIR models and their variations, which have both advantages and disadvantages. While they provide population-level views of system dynamics and are suitable at macro scales, they do not explicitly model individual elements (entities, agents, etc.) nor state transitions. Their mathematical formalism also has advantages in terms of numerical implementation and the possibility to examine mathematically a system's stability and robustness to externalities. Prior efforts to develop system dynamics models of specific aspects of these epidemics include medical or nonmedical use and trafficking of pharmaceutical opioids, effects of public health interventions on nonmedical opioid use, and heroin recovery as a function of treatment resources (Wakeland, Nielsen, and Schmidt 2012, White and Comiskey 2007, Prosper et al. 2011, Stanoev, Trpevski, and Kocarev 2014, Hoffer, Bobashev, and Morris 2009). Mathematical epidemiology methods also have been used more broadly to model other types of concurrent contagions on networks.

To provide some insight into our differential equation models, Figure 4 summarizes their general logic pseudocode, state variables, and inputs. The full model contains 84 state variables, 15 input variables, 84 coupled equations, and 955 lines of code based on governing dynamics of the below general type, using the notation defined in Figures 4b-c:

$$\dot{u} = hr * s + mr * r - (ap + cp + hi(s) + mi(r)) * u + (1 - amt) * v + ct * w$$
$$\dot{v} = ap * u - v$$
$$\dot{w} = cp * u - (cmt + ct) * w$$
$$\dot{r} = amt * v + cmt * w - (mht(u, v, w, r, s) + mor + mr) * r + mi(r) * u$$
$$\dot{s} = mht(u, v, w, r, s) * r - (hor + hr) * s + hi(s) * u$$
$$\dot{z} = mor * r + hor * s$$

Primary state variables at time t include the size of the opioid-free population $u(t)$, individuals on acute $v(t)$ or chronic $w(t)$ pain prescriptions, opioid misusers $r(t)$, heroin users $s(t)$, and fatal overdoses $z(t)$. Transition mechanisms between these states were identified or inferred from the medical literature; e.g., opioid-to-heroin transitions were coded as a function of supply-vs-demand for prescription opioids. Impacts of changes in social attitudes, heroin potency, and prescription rates also were incorporated along with coupling to similar equations and state variables for each adjacent region socially influencing prescription misuse and heroin use behaviors in the others. Heroin spread between regions was modeled by a threshold function with abuse initiated in heroin-free regions once the sum of heroin saturations of all neighboring regions exceeds user-input thresholds. While for illustration the simpler single-region single-drug model was implemented in VenSim (see causal loop diagram, Figure 3a), the full multi-region/multi-drug model was developed in research level code given its complexity and size.

2.3 Agent-Based Models

In addition to the above ODE models, we also developed two types of agent-based models (ABMs), namely cellular automata (CA) and social network analysis (SNA) models of between-region and between-person spread. ABMs follow a more 'bottom-up' framework in which individual units act according to a set of rules (deterministic or stochastic), with the state of each unit (entity) updated iteratively over time as functions of neighboring or otherwise connected entities or nodes. Classical ABM methods include cellular automata models characterized by physical locations adjacent to each other on a grid or lattice, network models characterized by nodes connected to each other through relationships and communication channels, and hybrid models that exhibit a combination of these characteristics. While cellular automata constructs

(a) **Begin ODE Pseudo-code**;

```
Read inputs from spreadsheet
Initialize state & input matrices
For each time step
  For each region
    For each sub-population
     Update ODEs
       Compute total social influence
         clean → opioid, heroin abuse
       Update acute, chronic patients
       Update illicit market supply
       Transition opioid licit users:
         acute → abuse, heroin, clean; chronic → abuse, heroin, clean
       Transition abusers:
         opioid → heroin, clean, death; heroin → opioids, clean, death
       If illicit demand > supply (any)
         abuse → switch, clean, death
    Next sub-population
    Compute total death region R
  Next region
  Compute total death time T
Next time step
Output results
End;
```

(b) **State variables** (dynamic over time *t* for each region)

$u(t)$	Drug-free population
$v(t)$	Acute pain opioid prescription population
$w(t)$	Chronic pain opioid prescription population
$r(t)$	Opioid illicit users
$s(t)$	Heroin illicit users
$x(t)$	Fatal overdoses

(c) **Model input rates**

		Value
ap	Acute prescribing	.03-.15
cp	Chronic prescribing	.03-.15
hr	Heroin abuse recovery	.01-.10
mr	Opioid abuse recovery	.08-.15
ct	Chronic termination	.30-.38
cmt	Chronic-to-abuse trans	.15-.30
amt	Acute-to-abuse transition	.01-.05
hor	Heroin overdose risk	.0049-.0066
mor	Opioid abuse overdose	.0010-.0012
mht	Drug seeking rate	.3-.7
mi	Misuse influence	80-200
hi	Heroin influence	800-2000

Figure 4: ODE model summary (84 state variables, 15 input variables, 84 coupled equations, 955 lines of code): (a) general logic pseudo-code, (b) dynamic state variables, (c) input scenario rate variables.

typically are useful to represent regional spread and evolution (Pfeifer et al. 2008), network diffusion constructs can effectively capture social influences, person-to-person spread, and within-population network topologies. While often easier to implement, such models can be more difficult to parametrize than ODEs and can present substantial computational requirements. Agent-based approaches have been used to model virus propagation over social networks of different topologies, and spatio-temporal spread of contagions or competing concurrent pathogens over geographic regions (Prakash et al. 2012, Ganesh, Massoulié, and Towsley 2005, Perez and Dragicevic 2009, Newman 2005). Flexible agent-based frameworks instantiable to a wide range of spread phenomena, including discrete equivalents of traditional SIR-like models, also recently have been, although this type of approach has not been used to study interdependent opioid and heroin abuse (Stanoev, Trpevski, and Kocarev 2014).

Figure 5 summarizes our SNA model logic, similar to co-pathogen spread and computer virus problems (Pastor-Satorras and Vespignani 2001, Kempe, Kleinberg, and Tardos 2003, El-Sayed et al. 2012), where nodes represent individuals or subpopulations connected via directed arcs weighted by adjacency or relationship strength. Our pilot CA model similarly updates 'neighbor' cells over time as functions of adjacent state variables, with adjacency defined via grid or lattice structures. In either case, topologies can be defined by geography or social connections, with common types of social networks including Erdős-Rényi, Barabási-Albert, and Watts-Strogatz (da Fontoura Costa and Andrade 2007). To-date we implemented pilot models of licit (S) and illicit (A) drug use levels at each node, updated each time step based on external total neighbor influences and internal reinforcement/decay mechanisms (denoted by G and M respectively). These mechanisms can be binary or continuous (e.g. degree to which individual or sub-population abuses a drug) relative to some threshold r, the former represented by governing equations of the type

$$S(y,t) = \max\left(S(y,t-1), \prod_{x\neq y}\left[1-\left(S(x,t-1)SP(x,y)\right)\right] > r\right) \text{ and}$$
$$A(y,t) = \max\left(S(y,t-1), \prod_{x\neq y}\left[1-\left(S(x,t-1)SP(x,y)AP(x,y)\right)\right] > r\right)$$

and the latter by

$$S(y,t) = \min\left(\left[S(y,t-1)M(y) + \Sigma_{x\neq y}S(x,t-1)SP(x,y)\right], 1\right) \text{ and}$$
$$A(y,t) = \min\left(\left[A(y,t-1)G(y) + \Sigma_{x\neq y}S(x,t-1)SP(x,y)AP(x,y)\right], 1\right).$$

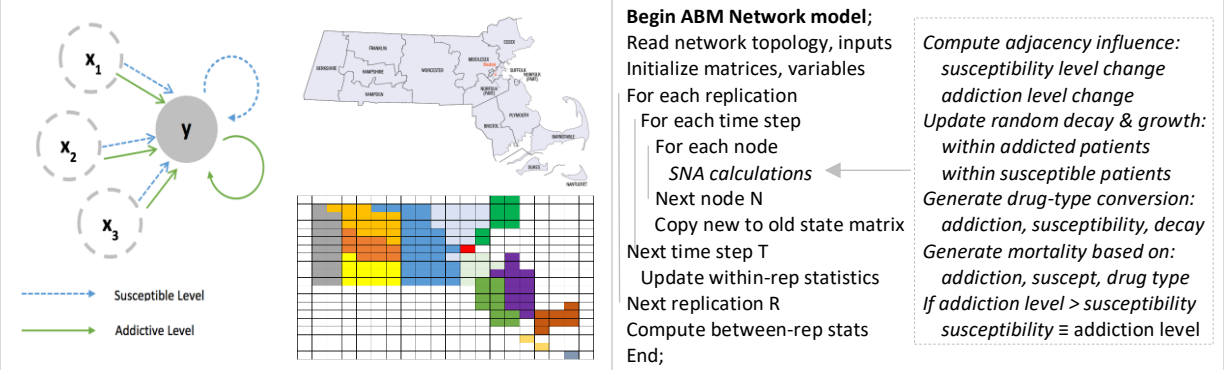

Figure 5: Overview of (left) general logic mechanisms and (right) pseudo-code for agent-based network opioid/heroin epidemic model (790 lines of code).

Three network spread model variations were developed to represent different node definitions and modeling scales: binary where both *S* and *A* levels are restricted to the integers 0 or 1 corresponding to individual no-use/use patterns; mixed where *S* is allowed to take real values between 0 and 1 corresponding to a more general definition of exposure and awareness; and continuous where both variables are real values between 0 and 1 corresponding to the proportion of users within a node's internal populations. Important aspects of these models include the effects of additional drugs (primarily fentanyl), treatment availability, street availability, relative pricing, mortality awareness, stochastics, and population variability. We so far assume homogeneous populations (socio-economics, addiction risks, transition rates, etc.), although we plan to introduce further stochastics and revisit all model assumptions with key stakeholders to ensure we are appropriately capturing all important considerations and dynamics.

3 RESULTS

3.1 Model Validation and Preliminary Results

Figures 6 and 7 summarize pilot results, illustrating both model face-validity and the potential to inform effective interventions and avoid unintentionally harmful policies. ODE model-generated annual mortality across Massachusetts counties (Figure 6a) closely replicates empirical data from 2000-2015 (Figure 1) with trends in abuse and death rates associated with each drug also agreeing with media reports. Agent-based results also are starting to produce face-validity, with rational within and between region epidemic growth and spread patterns across geographic and social networks (Figure 7). Applications of the agent based model to simulated networks of various sizes and architectures (Figure 3b) using similar parameters resulted in a broad range of growth and spread patterns that domain subject matter experts felt appear reasonable. Network types tested included 2-dimensional lattices of the type used in cellular automata models to map geographical adjacency, as well as graph-based models of real-world phenomena such as small-world clustering or preferential attachment effects.

3.2 Policy and Intervention Analysis

In terms of effective interventions, a combination of increased addiction treatment and reduced chronic pain prescribing appears to have the greatest impact (Figure 6b) whereas restricting acute pain prescribing, while frequently advocated (Dowell, Haegerich, and Chou 2016), without increased treatment options may significantly increase heroin mortality given its inexpensive availability (Office of the Surgeon General 2016). Interventions such as methadone maintenance therapy, treatment agreements, and urine testing (Starrels et al. 2010, Brennan et al. 2016) also have limited evidence in the literature of effectiveness if used alone. Moreover, combined interventions are likely to be more effective since restricted supply alone may cause individuals with untreated dependence to seek more dangerous alternatives (approximately 80% of heroin

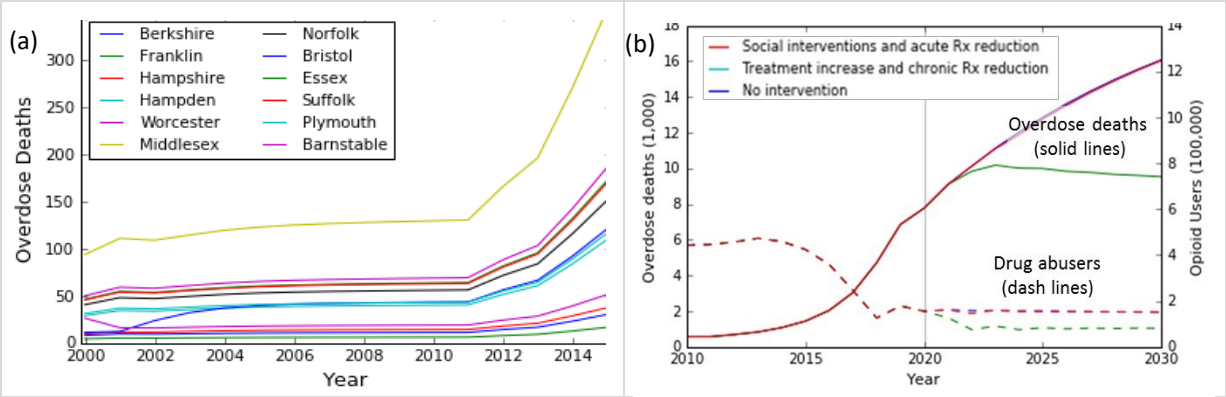

Figure 6: ODE model validation and illustration: (a) Model-based overdose deaths by MA county, 2000-2015; (b) Example of potential consequence of reduced acute opioid prescribing causing increased heroin mortality.

users start with opioid misuse; roughly 4% of prescription opioid abusers transition to heroin (National Center for Health Statistics 2016). While common interventions include prescription strength and duration limits, prescription drug monitoring programs (PDMPs), naloxone distribution, and safe storage and disposal (Haegerich et al. 2014), if not thoughtfully planned together with treatment or social interventions, stringent prescribing guidelines may create heroin/fentanyl markets and a worsening epidemic with associated mortality, economic, and social consequences. For example, in 2016 five states (NY, ME, MA, NH, IN) set 7-day maximums for first-time acute opioid or ED prescriptions (Massachusetts House of Representatives 2016, Maine Senate 2016, New York State Senate 2016) and Ohio began requiring physicians to check the state's PDMP before prescribing opioids beyond 7 days to prevent "doctor shopping", drug diversion, and fatal interactions with benzodiazepine sedatives (Ohio Department of Mental Health Services and Addiction 2016).

The agent-based network model produced similar results and insights. Figure 7b illustrates the opioid mortality rates among high school students into their early 20s by source of addiction initiation (acute prescribing, chronic prescribing, nonmedical) versus the potential decrease in each from introduction of various targeted interventions (solid lines), suggesting 50-75% reductions. Proposed potential interventions include legislative limits on prescription strength and duration, pushes for increased prescriber and patient

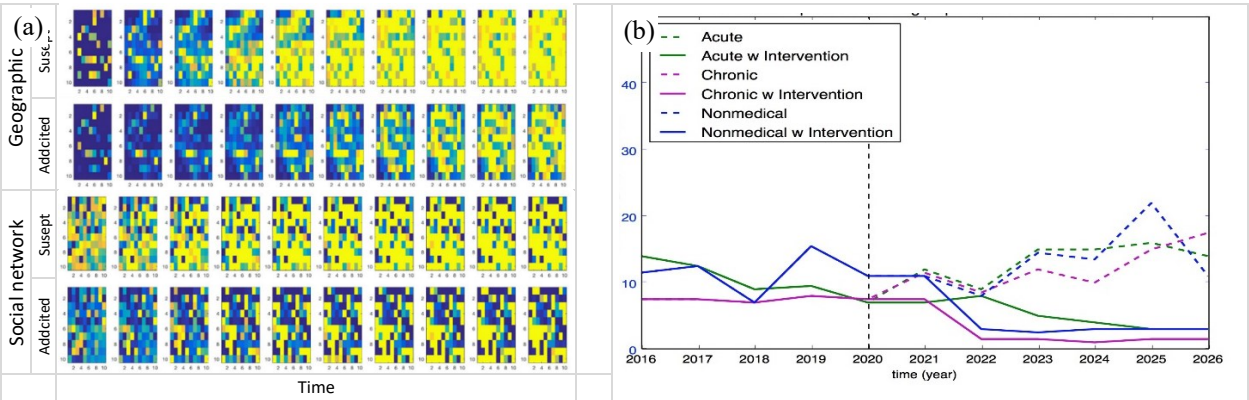

Figure 7: Agent-based network spread results. (a) Susceptibility and addiction levels across nodes and time steps for simulated networks with geographic lattice-based (top rows) vs. social preferential attachment (bottom rows) topologies. (b) Potential impact on reducing heroin mortality of acute, chronic, and nonmedical interventions implemented in 2020 (solid lines) versus if no interventions (dashed lines).

transparency, prescription and drug monitoring programs, naloxone distribution, and safe storage and disposal (Haegerich et al 2014). Such regulatory measures are thought to reduce unused opioid medications and prevent drug diversion for nonmedical use. Legislative reform and opioid regulation approaches, however, may have unintended consequences. For example, individuals with untreated dependence may switch to cheaper but more dangerous drugs to avoid detection; roughly 4% of individuals misusing prescription opioids transition to heroin, while 80% of heroin users started with opioid misuse (Office of the Surgeon General 2016). Stringent prescribing guidelines also may provide significant market opportunities for heroin, which is cheaper, more easily available, and has higher overdose death rates. More broadly, these results illustrate how such approaches can be used to gain insights into the interdependent mechanisms through which nonmedical prescription opioid use and heroin use propagate within and between communities.

3.3 Hypothesis Generation, Parameter Search, and Computational Issues

Model parameterization and computational issues are being approached as follows. Due to significant uncertainty in parametrization, we conducted a sensitivity analysis to determine which parameters had the greatest systemic impact. We then performed a multi-dimensional search on the five most sensitive parameters, comparing model outputs to historical overdose deaths, aiming to maximize the agreement between model predictions and empirical data (as quantified by the mean squared error). This analysis was replicated across data sets (using overdose counts from both all of the Commonwealth of Massachusetts and only Barnstable county on Cape Cod), and was run separately piecewise for the 2000-2012 and 2012-2015 intervals, since historical data suggest significant changes in overdose dynamics from 2012 onwards. Figure 8a summarizes run times for one replication of the agent based network model with an increasing number of nodes, which as shown tends to increase exponentially as the model approaches realistic sizes.

Figures 8b and 8c similarly summarize brute force times to estimate key parameters identified through factorial screening, which increase non-linearly as a function of the number of parameters searched on. A more extensive search would require increased computational power or more advanced optimization algorithms as described above. We also are starting to use the models in more theoretic manners to produce insight and inference, such as within a hypothesis generation approach to identify the top *K* parameterization vectors that best explain historical data from any region or regions. The general idea is to review these results with subject matter experts for discussion, plausibility, and meaning. We also have started to use

a. SNA model run times

Nodes	Steps	CPU secs	Memory MB
20	20	0.9	304
20	100	3.6	342
20	300	19.2	336
40	20	2.7	348
40	100	10.1	374
40	300	37.2	393
80	20	49.1	985
80	100	112	956
80	300	270	1130
100	20	334	2516
100	100	510	2538
100	300	1071	2793

b. ODE parameter search

Search terms	Steps	CPU secs	Memory MB
1	10	.003	0.4
1	100	.02	0.6
1	1000	.185	0.6
2	10	.021	0.6
2	100	1.93	1.7
2	1000	191.4	155
3	10	.187	0.6
4	10	1.897	1.8
5	10	19.42	23.2
6	10	194.4	158
7	10	11005	3104
8	10	n/a	error

(c)

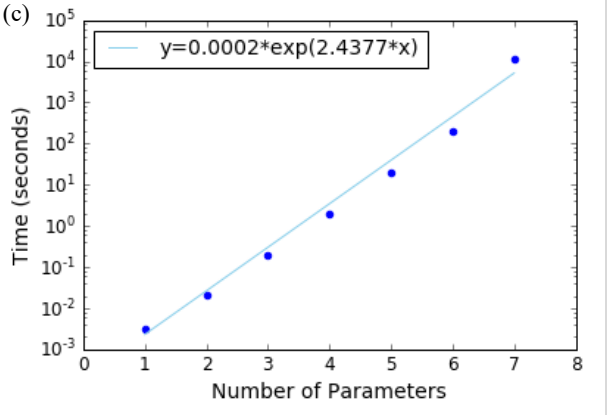

Figure 8: Computational requirements: (a) Agent-based mode as a function of model size, (b)-(c) Parameter search optimization on ODE model as function of number of search parameters and model size.

structural versions of the ODE models to explore if certain theoretic properties (stability, reproductive number, endemic equilibria, bifurcation, and so on) can be shown to exist or to identify conditions under which they exist, which also could inform policy making in important manners.

4 DISCUSSION

Substance abuse epidemics have existed for centuries, but none perhaps as devastating, widespread, and heartbreaking as the current opioid and heroin crises that are affecting nearly all population strata nationwide and abroad. Effective local and policy interventions, however, remain elusive and unclear. In other settings with complex causal, behavioral, social, and economic dynamics, system science methods and model abstraction have been useful for helping understand the overall context, interdependencies, and coupled logic chains. Such models also can be used to help develop insight, rapidly test large numbers of potential interventions, estimate underlying parameters and rates, identify interesting and important interactions, and generate and down-select a set of viable hypotheses and policies for further evaluation. In the present context, the pilot models developed and described in this paper illustrate this potential utility to inform the current opioid crisis and help policy makers, clinicians, and treatment experts develop effective potential interventions.

As examples, this paper illustrated the potential impact of changes in opioid prescribing patterns, social interventions, addiction treatment capacity expansion, and others. To our knowledge this is among the first research to develop multi-substance multi-scale models of this type and to consider interdependent abuse of multiple substances. While model-informed policy development has been conducted in a range of traditional epidemiology applications (Halasa et al, 2013, Mishra et al, 2014) and some efforts have modeled opioid or heroin use independently, little has been done to integrate these two aspects into a comprehensive model (Hoffer, Bobashev, and Morris, 2009). Furthermore, much like the well-meaning "managing pain as the fifth vital sign" healthcare campaign appeared to be important to promote widely, models of the types described here can help identify potential unintended negative consequences of ideas that initially appear logical. In our case, the negative effects of law interventions to interrupt heroin distribution and of reducing opioid prescribing – without co-investment to prevent fentanyl distribution and build treatment capacity – are good examples of this "squeeze the bubble" phenomenon.

While our analysis to-date has focused on just two geographic settings as proof-of-concept (all counties within Massachusetts, all towns within Barnstable county), future work will include additional populations across the country, under different assumptions, and at multiple scales, as well as incorporate additional modeling details, heterogeneity, and sources of random behavior, such as via stochastic differential equations, influence accumulation, and decision-to-abuse thresholds. Qualitative ethnography methods, adopted from health service research, also are proving very useful for model development, identification of important process logic details, and to provide insight to historical spread patterns that can inform intervention design. Two major technical challenges to-date have included model parameterization and calibration, primarily due to data availability issues, and computational requirements for large-scale agent-based models and parameter estimation search routines. To address and mitigate these issues, we are collaborating with additional domain experts to identify initial values and confidence intervals for measures not addressed in the literature, are exploring more efficient techniques for large matrix storage and algebra, and are developing more advanced, non-exhaustive search algorithms.

5 CONCLUSION

This paper described the development, validation, and preliminary use of analytic simulation models (system dynamics, agent-based, cellular automata) of the geographic-temporal spread of the inter-related opioid and heroin epidemics gripping the U.S. The overall intent is to use these models to help policy makers analyze and optimize effective combinations of interventions. As shown, these models can reasonably replicate the epidemic to-date both over time and region-to-region, and thus can complement other efforts to limit this national public health crisis, and reduce regional and population disparities, given greater abuse

of cheaper/worse drugs among lower socio-economic groups. More broadly, results can significantly improve the understanding of substance abuse epidemics from a systems perspective and accelerate effective policy and intervention strategy discovery. Ultimately our hope is to contribute to the identification of effective combinations of policies and interventions that reduce the heartbreaking suffering, mortality, and costs from these and similar future epidemics.

ACKNOWLEDGMENTS

This research was partially supported by the National Science Foundation (grant IIP-1034990), although any views expressed here are those of the authors and do not necessarily reflect those of the NSF.

REFERENCES

Brennan, P. L., A. C. Del Re, P. T. Henderson, and J. A. Trafton. 2016. "Healthcare System-Wide Implementation of Opioid-Safety Guideline Recommendations: The Case of Urine Drug Screening and Opioid-Patient Suicide and Overdose-Related Events in the Veterans Health Administration." *Translational Behavioral Medicine* 6(4):605-612.

Center for Disease Control and Prevention. 2013. "Opioids Drive Continued Increase in Drug Overdose Deaths." National Center for Health Statistics, accessed July 20. https://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html.

da Fontoura Costa, L., and R. F. S. Andrade. 2007. "What are the Best Concentric Descriptors for Complex Networks?" *New Journal of Physics* 9(9):311.

Dowell, D., T. M. Haegerich, and R. Chou. 2016. "CDC Guidelines for Prescribing Opioids for Chronic Pain." Center for Disease Control and Prevention, accessed July 20. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm#suggestedcitation.

El-Sayed, A. M., P. Scarborough, L. Seemann, and S. Galea. 2012. "Social Network Analysis and Agent-Based Modeling in Social Epidemiology." *Epidemiologic Perspectives & Innovations* 9(1):1.

Florence, C. S., C. Zhou, F. Luo, and L. Xu. 2013. "The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States." *Medical Care* 54(10):901-906.

Ganesh, A., L. Massoulié, and D. Towsley. 2005. "The Effect of Network Topology on the Spread of Epidemics." In *INFOCOM 2005. Proceedings of the 24th Annual Joint Conference of the IEEE Computer and Communications Societies*, IEEE.

Haegerich, T. M., L. J. Paulozzi, B. J. Manns, and C. M. Jones. 2014. "What We Know, and don't Know, About the Impact of State Policy and Systems-Level Interventions on Prescription Drug Overdose." *Drug and Alcohol Dependence* 145:34-47.

Halasa, T., P. Willeberg, L. E. Christiansen, A. Boklund, M. AlKhamis, A. Perez, and C. Enøe. 2013. "Decisions on Control of Foot-and-Mouth Disease Informed Using Model Predictions." *Preventive Veterinary Medicine* 112(3):194-202.

Hoffer, L. D., G. Bobashev, and R. J. Morris. 2009. "Researching a Local Heroin Market as a Complex Adaptive System." *American Journal of Community Psychology* 44(3-4):273-286.

Kempe, D., J. Kleinberg, and É. Tardos. 2003. "Maximizing the Spread of Influence through a Social Network." In *Proceedings of the Ninth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, 137-146.

Maine Senate. 2016. "An Act to Prevent Opiate Abuse by Strengthening the Controlled Substances Prescription Monitoring Program." accessed July 20. https://legislature.maine.gov/legis/bills/getPDF.asp?paper=SP0671&item=1&snum=127.

Massachusetts House of Representatives. 2016. "An Act Relative to Substance Use, Treatment, Education and Prevention." accessed July 20. https://malegislature.gov/Bills/189/House/H4056.

Mishra, S., M. Pickles, J. F. Blanchard, S. Moses, Z. Shubber, and M. C. Boily. 2014. "Validation of the Modes of Transmission Model as a Tool to Prioritize HIV Prevention Targets: A Comparative Modelling Analysis." *PLoS One* 9(7):e101690.

National Center for Health Statistics. 2016. "Underlying Cause of Death 1999-2015." CDC Wonder: Center for Disease Control and Prevention, accessed July 20. https://wonder.cdc.gov/.

New York State Senate. 2016. "Relates to the Treatment of Heroin and Opioid Addictions." accessed July 20. https://www.nysenate.gov/legislation/bills/2015/s8139/amendment/original.

Newman, M. E. J. 2005. "Threshold Effects for Two Pathogens Spreading on a Network." *Physical Review Letters* 95(10):108701.

Office of the Surgeon General, U.S. Department of Health and Human Services. 2016. "Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health." U.S. Department of Health and Human Services, accessed July 20. https://addiction.surgeongeneral.gov/surgeon-generals-report.pdf.

Ohio Department of Mental Health Services and Addiction. 2016. "Summary: Progressive Opioid Prescribing Guidelines for a Safer Ohio." accessed July 20. http://mha.ohio.gov/Portals/0/assets/Initiatives/GCOAT/20160112-GCOAT-Prescribing-Guidelines-Summary.pdf.

Pastor-Satorras, R., and A. Vespignani. 2001. "Epidemic Spreading in Scale-Free Networks." *Physical Review Letters* 86(14):3200.

Perez, L., and S. Dragicevic. 2009. "An Agent-Based Approach for Modeling Dynamics of Contagious Disease Spread." *International Journal of Health Geographics* 8(1):50.

Pfeifer, B., K. Kugler, M. M. Tejada, C. Baumgartner, M. Seger, M. Osl, M. Netzer, M. Handler, A. Dander, and M. Wurz. 2008. "A Cellular Automaton Framework for Infectious Disease Spread Simulation." *The Open Medical Informatics Journal* 2:70.

Prakash, B. A., D. Chakrabarti, N. C. Valler, M. Faloutsos, and C. Faloutsos. 2012. "Threshold Conditions for Arbitrary Cascade Models on Arbitrary Networks." *Knowledge and Information Systems* 33(3):549-575.

Prosper, O., O. Saucedo, D. Thompson, G. Torres-Garcia, X. Wang, and C. Castillo-Chavez. 2011. "Modeling Control Strategies for Concurrent Epidemics of Seasonal and Pandemic H1N1 Influenza." *Mathematical Biosciences and Engineering* 8(1):141-170.

Seal, K. H., M. Downing, A. H. Kral, S. Singleton-Banks, J. Hammond, J. Lorvick, D. Ciccarone, and B. R. Edlin. 2003. "Attitudes about Prescribing Take-Home Naloxone to Injection Drug Users for the Management of Heroin Overdose: a Survey of Street-Recruited Injectors in the San Francisco Bay Area." *Journal of Urban Health* 80(2):291-301.

Stanoev, A., D. Trpevski, and L. Kocarev. 2014. "Modeling the Spread of Multiple Concurrent Contagions on Networks." *PloS One* 9(6):e95669.

Starrels, J. L., W. C. Becker, D. P. Alford, A. Kapoor, A. R. Williams, and B. J. Turner. 2010. "Systematic Review: Treatment Agreements and Urine Drug Testing to Reduce Opioid Misuse in Patients with Chronic Pain." *Annals of Internal Medicine* 152(11):712-720.

The State of Maryland. 2017. "Declaration of a State of Emergency, Executive Order 01.01.2017.04." accessed July 20. http://news.maryland.gov/mema/wp-content/uploads/sites/7/2017/03/0453_001.pdf.

Wakeland, W., A. Nielsen, and T. D. Schmidt. 2012. "System Dynamics Modeling of Medical Use, Nonmedical Use and Diversion of Prescription Opioid Analgesics." In *Proceedings of the 30th International Conference of the Systems Dynamics Society*, edited by E. Husemann and D. Lane, St. Gallen, Switzerland.

White, E., and C. Comiskey. 2007. "Heroin Epidemics, Treatment and ODE Modelling." *Mathematical Biosciences* 208(1):312-324.

AUTHOR BIOGRAPHIES

JAMES BENNEYAN is a Professor of Industrial Engineering and Operations Research and director of the Healthcare Systems Engineering Institute at Northeastern University. His research interests include probability models, simulation of all types, system design, and systems engineering application to important healthcare problems broadly. He is Past President of the industrial engineering Society for Health Systems and a Fellow of the Institute of Industrial Engineers, Healthcare Information and Management Systems Society, and Institute for Healthcare Improvement. His e-mail address is j.benneyan@northeastern.edu.

JACQUELINE GARRAHAN is an MS student in the Mathematics Department at Northeastern University, with a focus in healthcare operations research. She has a B.A. degree in Psychology and Physics from Boston College. Her research interests include differential equations, applied physics, and optimal control strategies applied to substance addiction problems. Her e-mail address is j.garrahan@northeastern.edu.

IULIAN ILIEŞ is postdoctoral research fellow in the Healthcare Systems Engineering Institute at Northeastern University. He holds a BS in Mathematics and Cognitive Psychology from International University in Bremen Germany and an MS in Mathematics and PhD in Statistics from Jacobs University. His research interests include data mining, machine learning, and stochastic dynamical systems. His e-mail address is i.ilies@northeastern.edu.

XIAOLI DUAN is a PhD student in Industrial Engineering and Operations Research at Northeastern University, with her a B.S. in Mathematics from the University of Minnesota. Her research interests include agent-based models, mathematical probability, and predictive models of complex healthcare problems. Her e-mail address is duan.xi@husky.neu.edu.