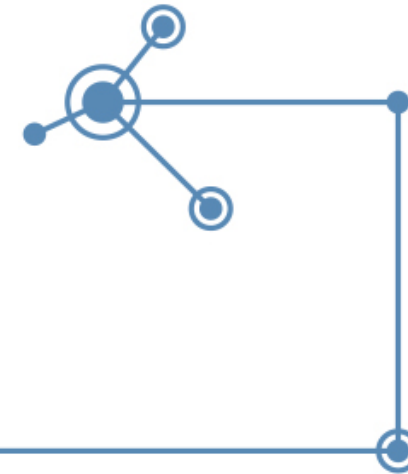


Resource optimization problems using a mathematical model of influenza



Srini Venkatramanan, PhD
Biocomplexity Institute of Virginia Tech

“In Flew Enza”

- Infectious diseases are among the leading causes of human mortality worldwide
- Seasonal Influenza in the United States
 - About 310,000 hospitalizations in 2015/16 season¹
 - Annual economic burden ~ \$87.1 billion
 - Estimated 61 million cases during 2009/10 pandemic²
- Spanish flu of 1918
 - ~20-40% of the world became ill, ~50 million deaths
 - 675,000 deaths in US during Sept 1918 - April 1919



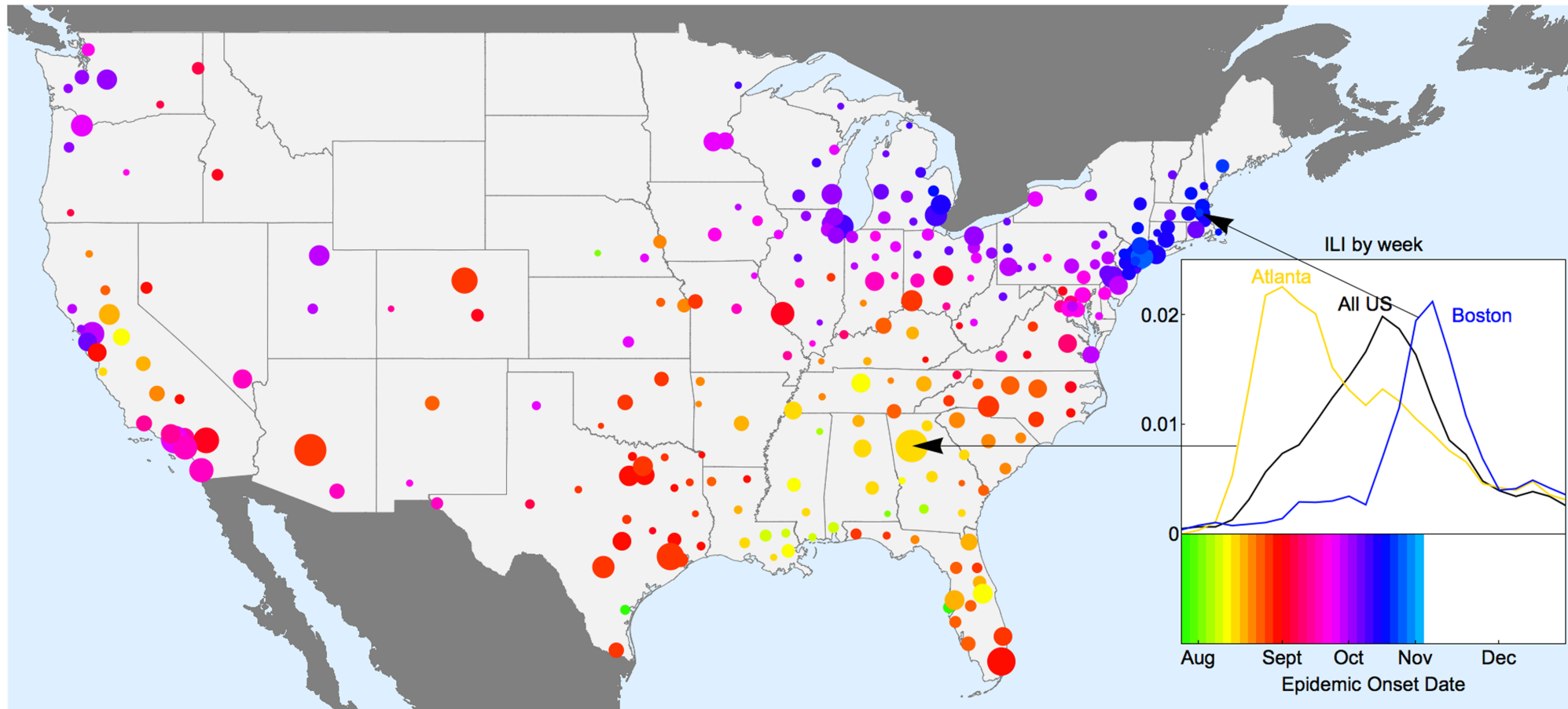
¹<https://www.cdc.gov/flu/about/qa/hospital.htm>

²https://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

How does influenza spread?

- Person to person (up to 6 feet away)
 - Droplets during cough, sneeze or talk reaching mouth/nose
 - Touching surface that has flu virus and then touching mouth/nose
 - Infectious: From 1 day pre-symptoms and up to 5-7 days post-sick.
- Key factors
 - Human contact, and hence human mobility
 - (Charu et al. 2017, PLOS CompBio)
 - Absolute humidity modulates airborne survival/transmission of virus
 - (Shaman et al. 2010, PLOS Bio)
- Typically occurs during Fall and Winter. Peaking mostly between December and February
- Has a noticeable geo-spatial trend across seasons: starting in the South East (Texas, Louisiana, Mississippi, Alabama, Georgia)

Spatial spread – 2009 H1N1

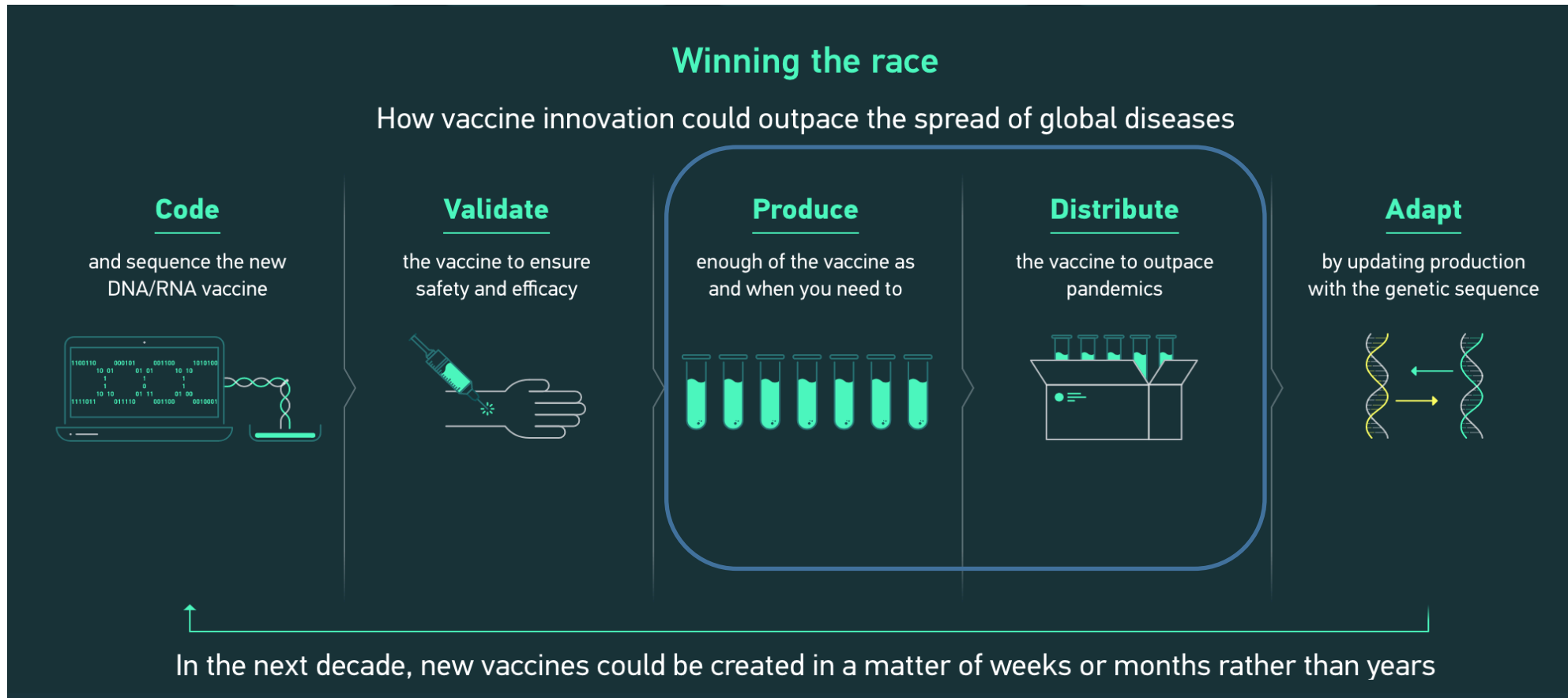


Source: Julia Gog et al. PLOS Comp Bio (2014)

Vaccines

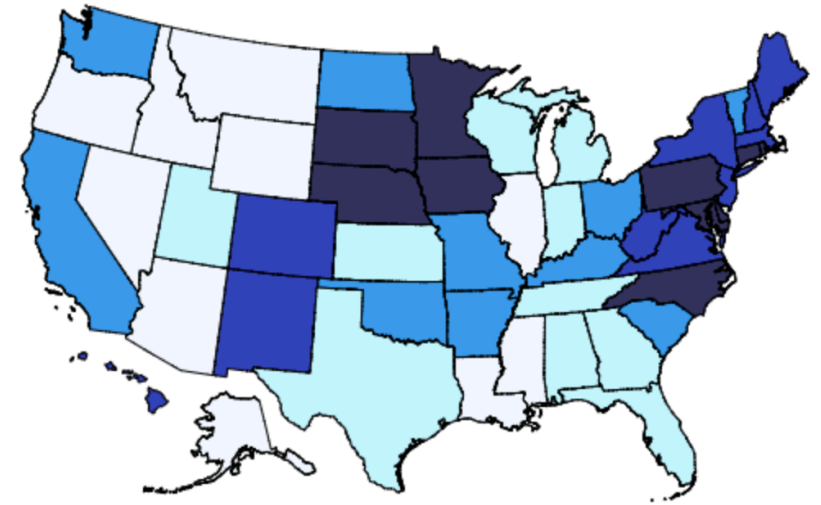
- Prophylactic vaccines help minimize the impact of the epidemic

Source: Mosaic Science – Outpacing Pandemics



Influenza vaccine in United States

- For 2017-18, trivalent vaccines are recommended to contain¹:
 - A/Michigan/45/2015 (H1N1)pdm09-like
 - A/Hong Kong/4801/2014 (H3N2)-like
 - B/Brisbane/60/2008-like (B/Victoria lineage)
- For 2016-17 Flu vaccine coverage
 - 59% among children, 43.3% among adults²
 - State-by-state variability in coverage
 - HP 2020 Target: 70%
- High cost of delivery logistics
- Supply limitations (esp. surge vaccines)



State-level variability

¹<https://www.cdc.gov/flu/about/season/current.htm>

²<https://www.cdc.gov/flu/fluview/>

Questions

Can we optimize the allocation of vaccines to minimize the epidemic impact?



Can we model the spatio-temporal spread of the epidemic?



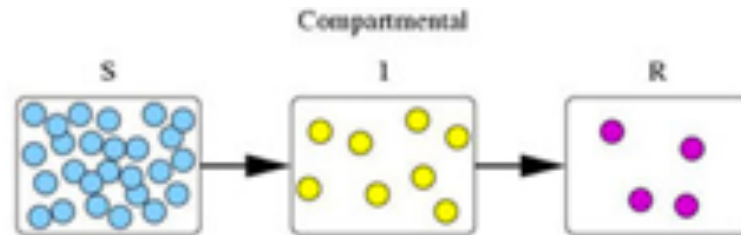
Can we capture human mobility at the national scale?

Related work

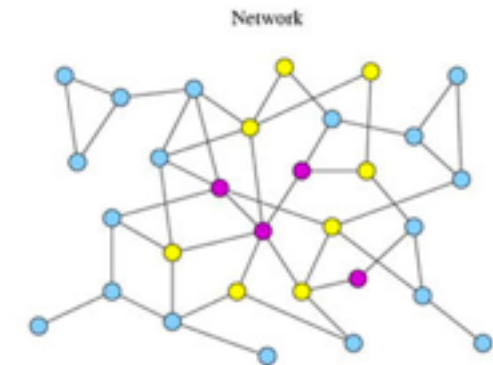
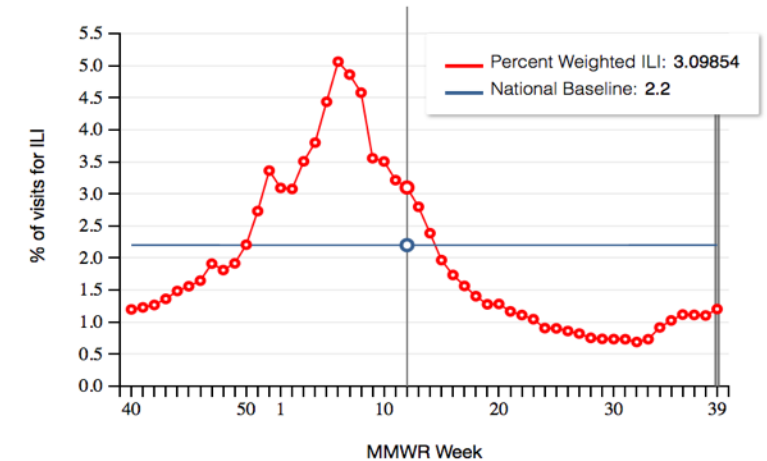
- Jan Medlock and Alison P. Galvani, “*Optimizing Influenza Vaccine Distribution*”, Science 2009
 - Analyzed an age-based compartmental model to identify optimal vaccine allocation
- Cecile Viboud et al., “*Synchrony, Waves, and Spatial Hierarchies in the Spread of Influenza*”, Science 2006
 - Analyzed the impact of long-range and short-range mobility on the spatial spread patterns of seasonal influenza
- Marcelo Gomes et al., “*Assessing the International Spreading Risk Associated with the 2014 West African Ebola Outbreak*”, PLOS Currents 2014.
 - Used a metapopulation model (GLEaM) that combines population and airline mobility data to assess spreading risk of Ebola in 2014.

Mathematical models for Influenza

- Statistical models
 - Time series analyses (e.g. seasonal ARIMA)
 - Recent ML approaches (RNN/LSTM)
 - Useful for short-term forecasts
 - Cannot capture interventions
- Mechanistic models
 - Capture the mechanism by which flu spreads
 - Could be compartmental or agent-based (network)



Percentage of visits for ILI, National Summary,
2016-17 Season, week ending Sep 30, 2017
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet
[Download Image](#) [Download Data](#) ?



4R's: Reason, Resolution, Reactions and Range

Possible solution

Greedy optimization for state level weekly vaccine allocation

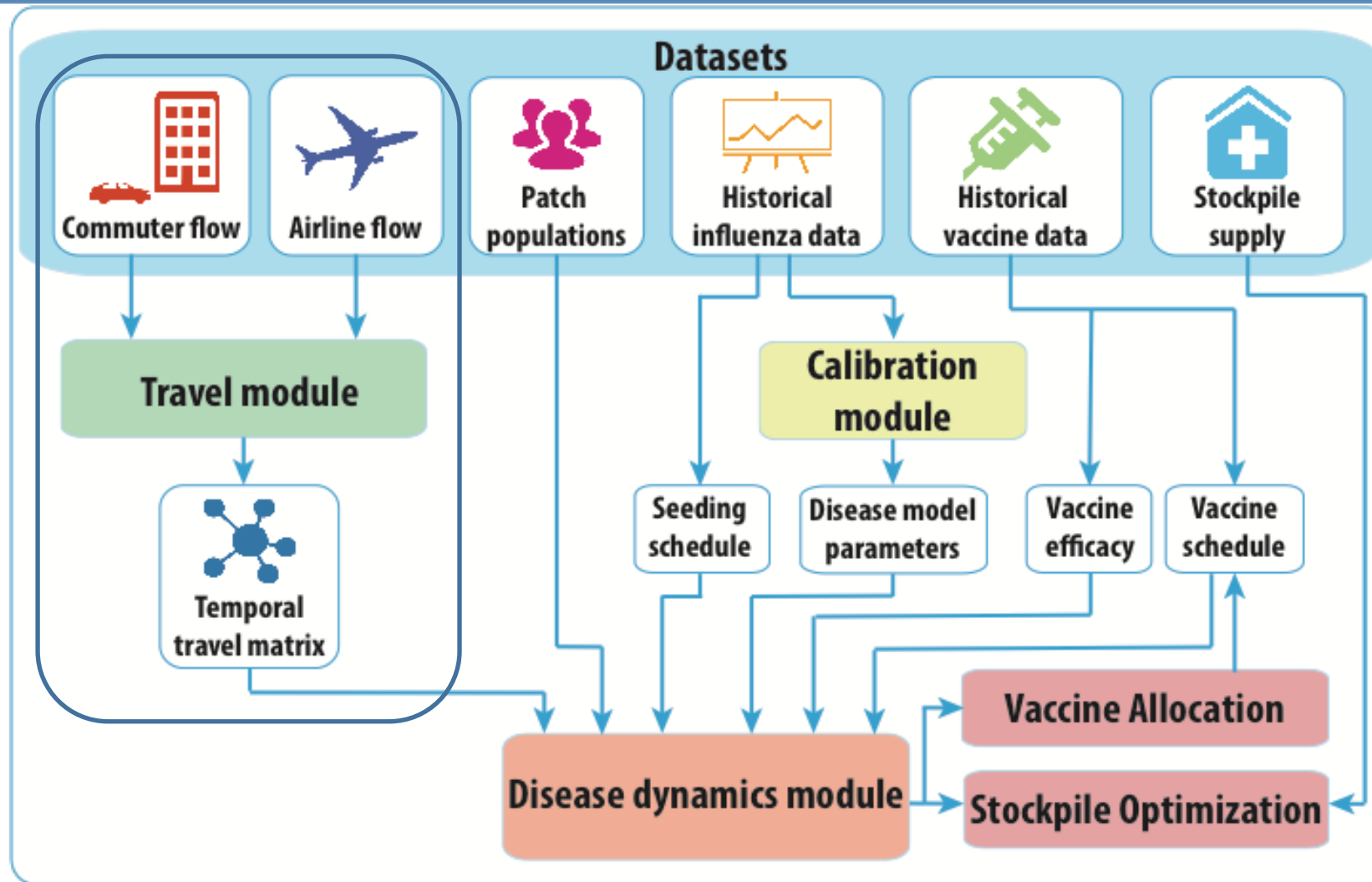


Metapopulation (patch) SEIR model for Flu simulation



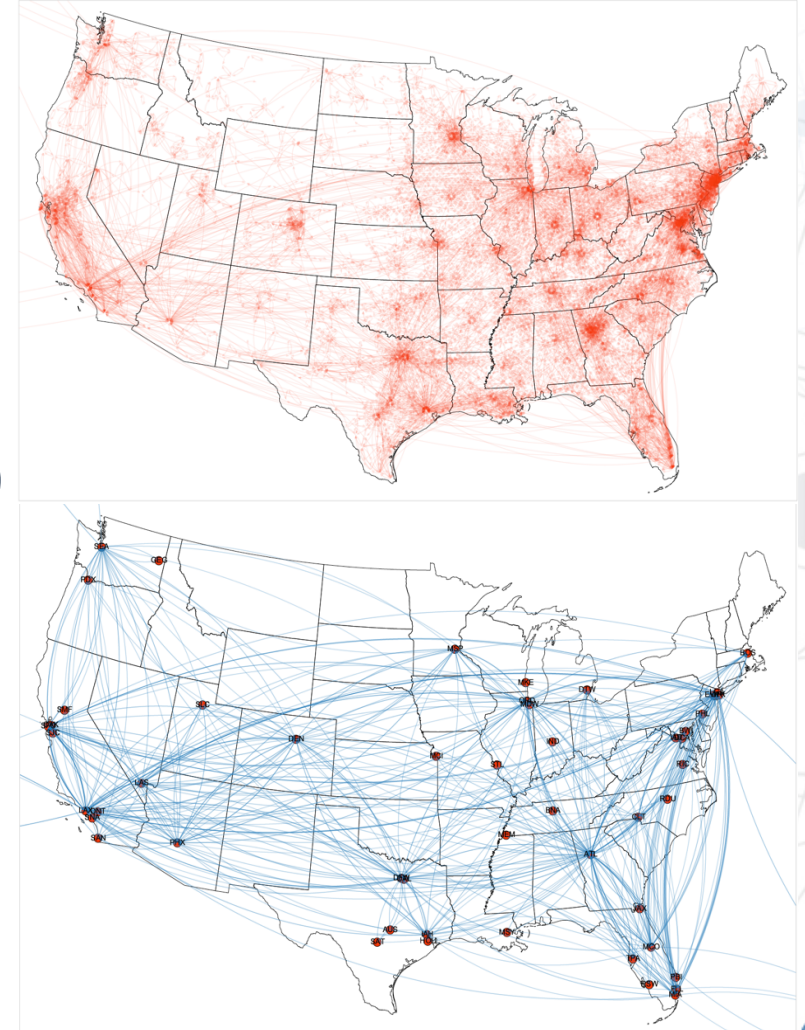
Temporal travel matrix between US counties

Our approach



Travel module - Datasets

- Commuter dataset (short-range, regular)
 - Source: American Community Survey¹
 - Number of commuters between a pair of counties on a typical day
- Domestic airline dataset (long-range, rare)
 - Source: Bureau of Transportation Statistics²
 - Number of passengers between two airports each month

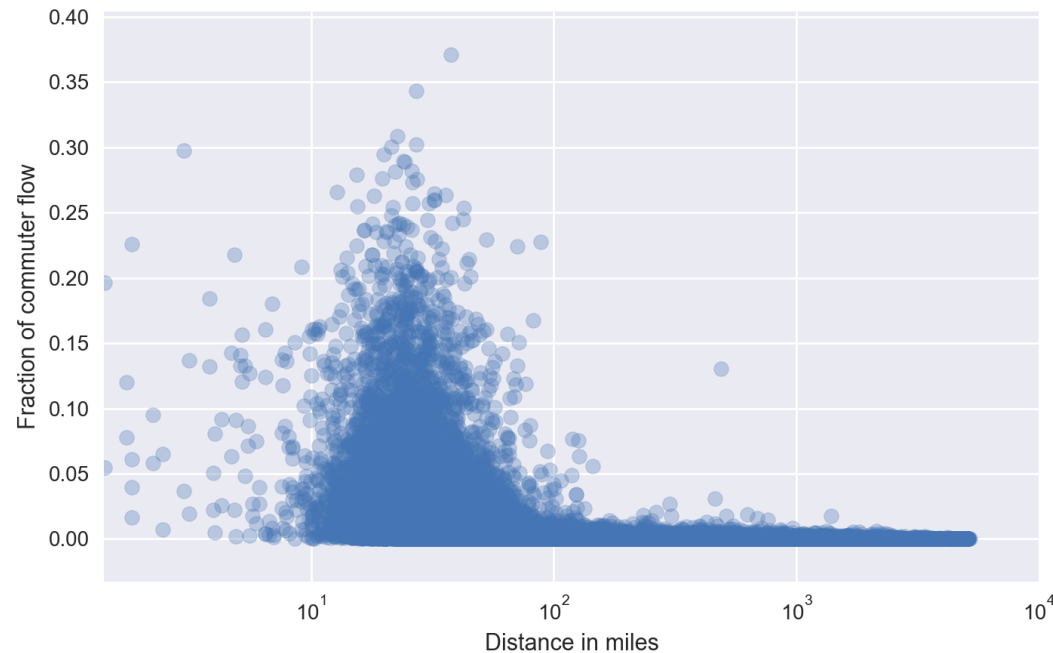


¹ <https://www.census.gov/programs-surveys/acs/>

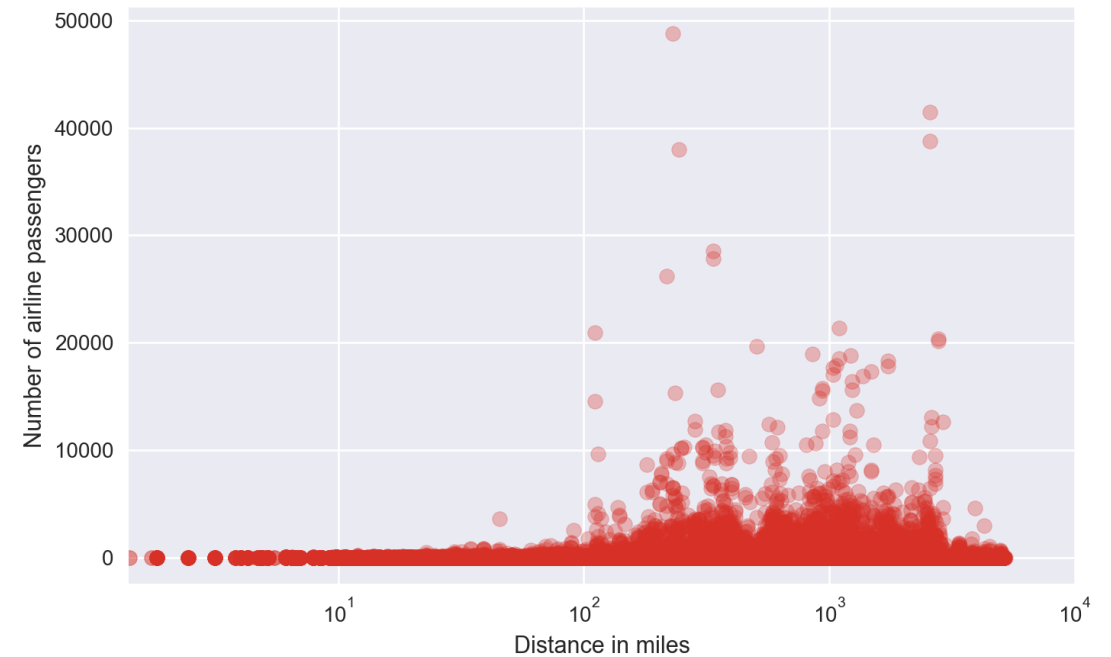
² https://www.rita.dot.gov/bts/data_and_statistics/

Travel data statistics

Commuting data



Domestic airline data



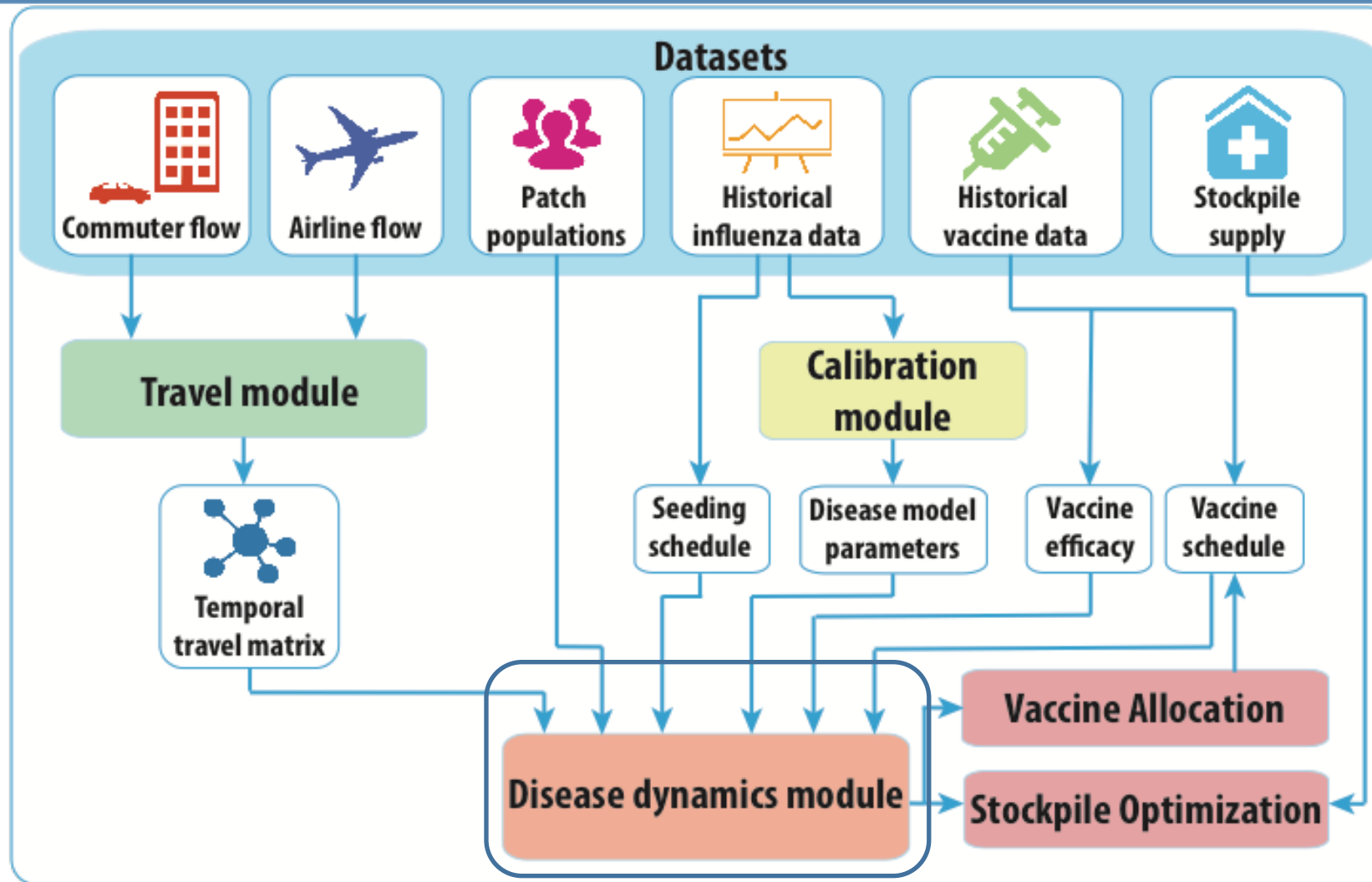
Travel module - Challenges

- Spatial mismatch
 - Need to disaggregate airline flows to county level
 - Define catchment area (120 miles) around the airport
 - Assign flows proportional to county area intersection
- Temporal mismatch
 - Airline travelers stay longer than commuters
 - Scale the travelers by average stay duration
- Combine and normalize

$$O_{ij}^m = C_{ij} + \Delta * A_{ij}^m$$
$$\Theta_{ij}^m = \begin{cases} \frac{O_{ii}^m + (P_i - \sum_j O_{ij}^m)}{P_i} & \text{if } i = j \\ \frac{O_{ij}^m}{P_i} & \text{otherwise} \end{cases}$$

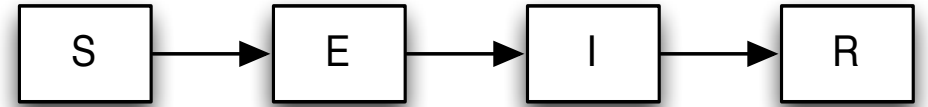
- Fraction of population of county i, in county j, on a typical day of month m

Our approach



Disease dynamics module

- Evolution within a county using the traditional SEIR (Susceptible -> Exposed -> Infected -> Recovered) ODE model



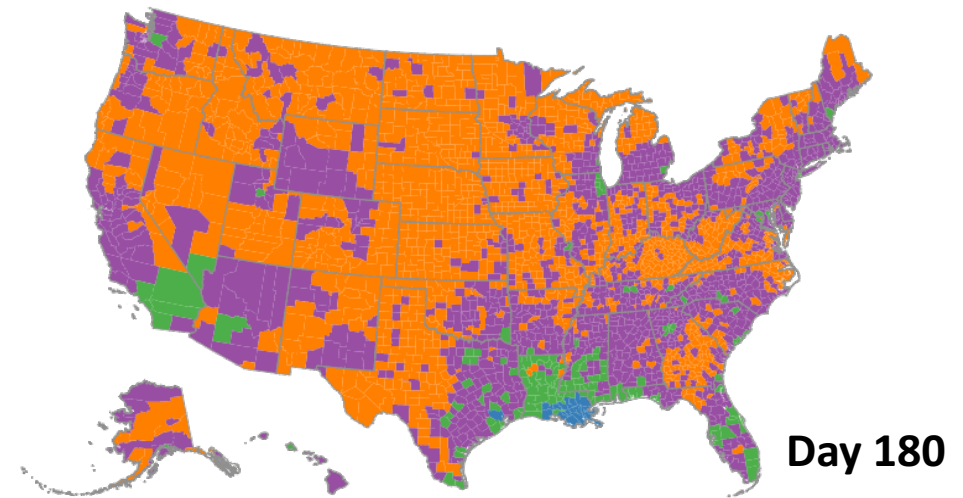
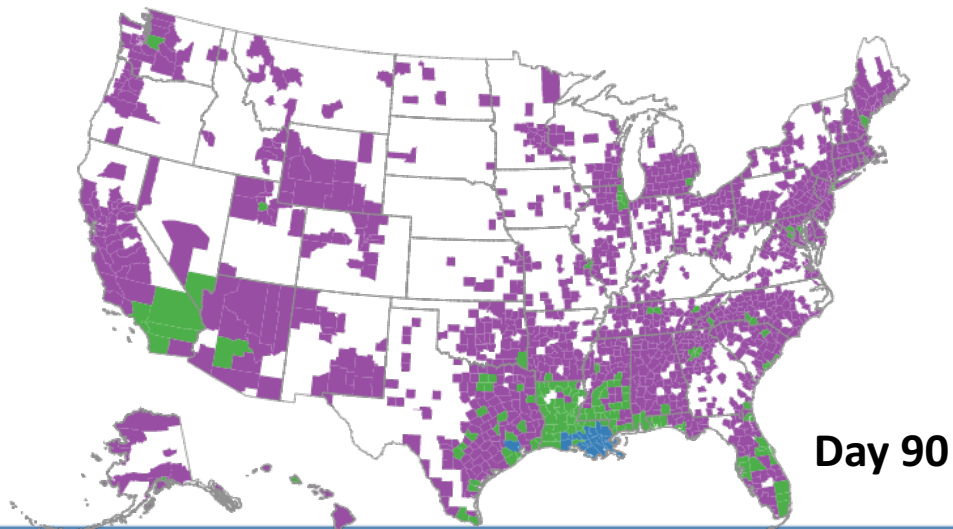
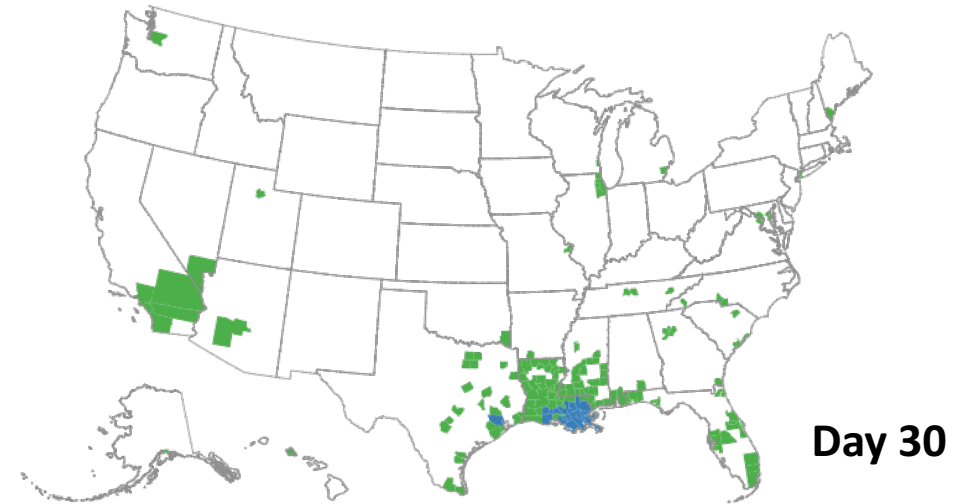
- Travel matrix for force of infection between patches

$$I_j^{\text{eff}} = \sum_i \Theta_{ij} I_i; \quad N_j^{\text{eff}} = \sum_i \Theta_{ij} N_i$$

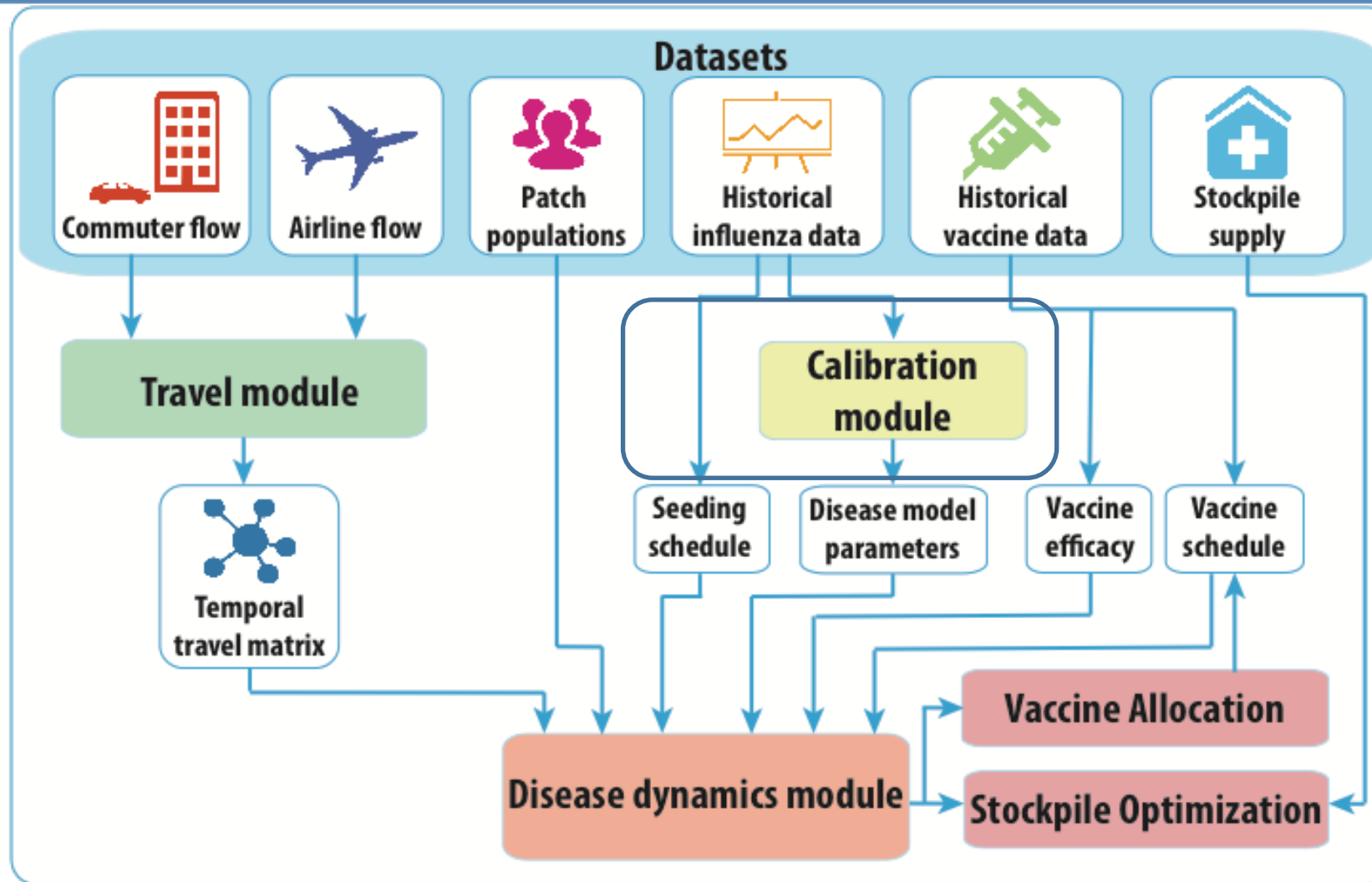
- Include vaccination state (S -> V)

$$\begin{aligned} \frac{dS_i}{dt} &= -\beta S_i(t) \frac{I_i(t)}{N_i} \\ \frac{dE_i}{dt} &= \beta S_i(t) \frac{I_i(t)}{N_i} - \alpha E_i(t) \\ \frac{dI_i}{dt} &= \alpha E_i(t) - \gamma I_i(t) \\ \frac{dR_i}{dt} &= \gamma I_i(t) \end{aligned}$$

Sample spatio-temporal spread

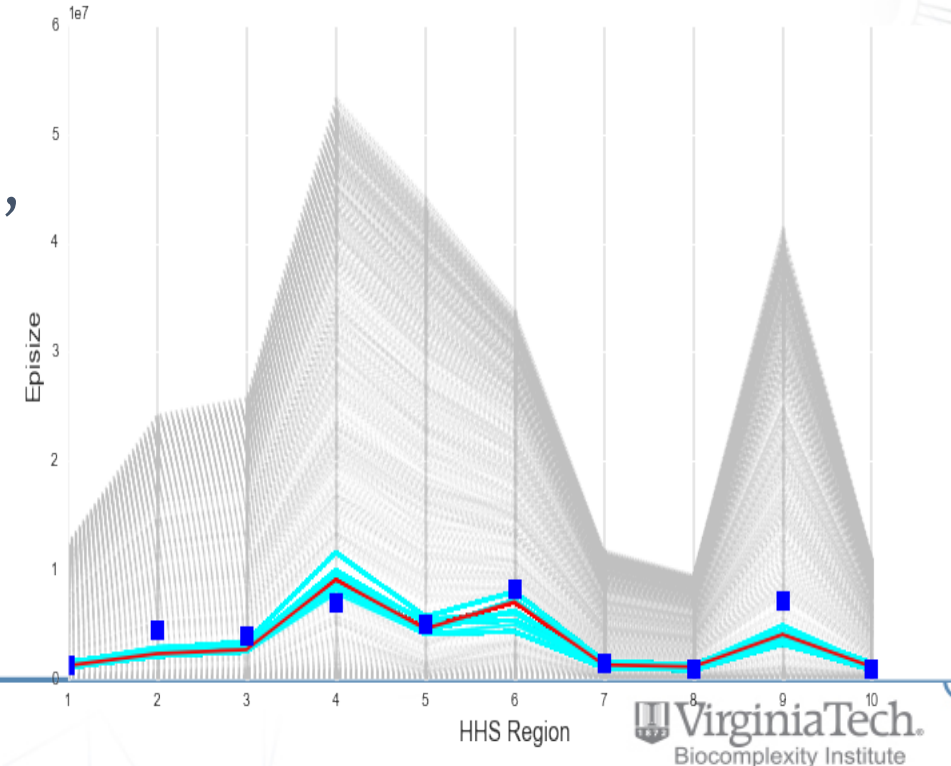
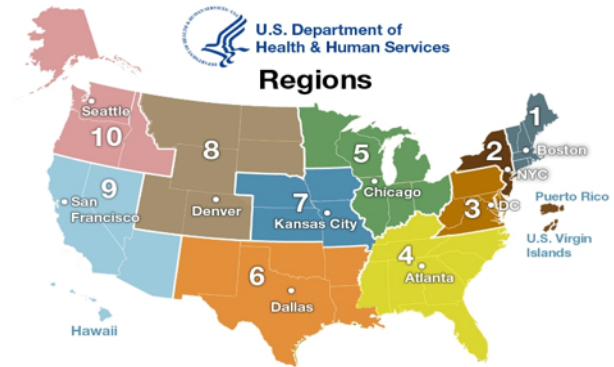


Our approach

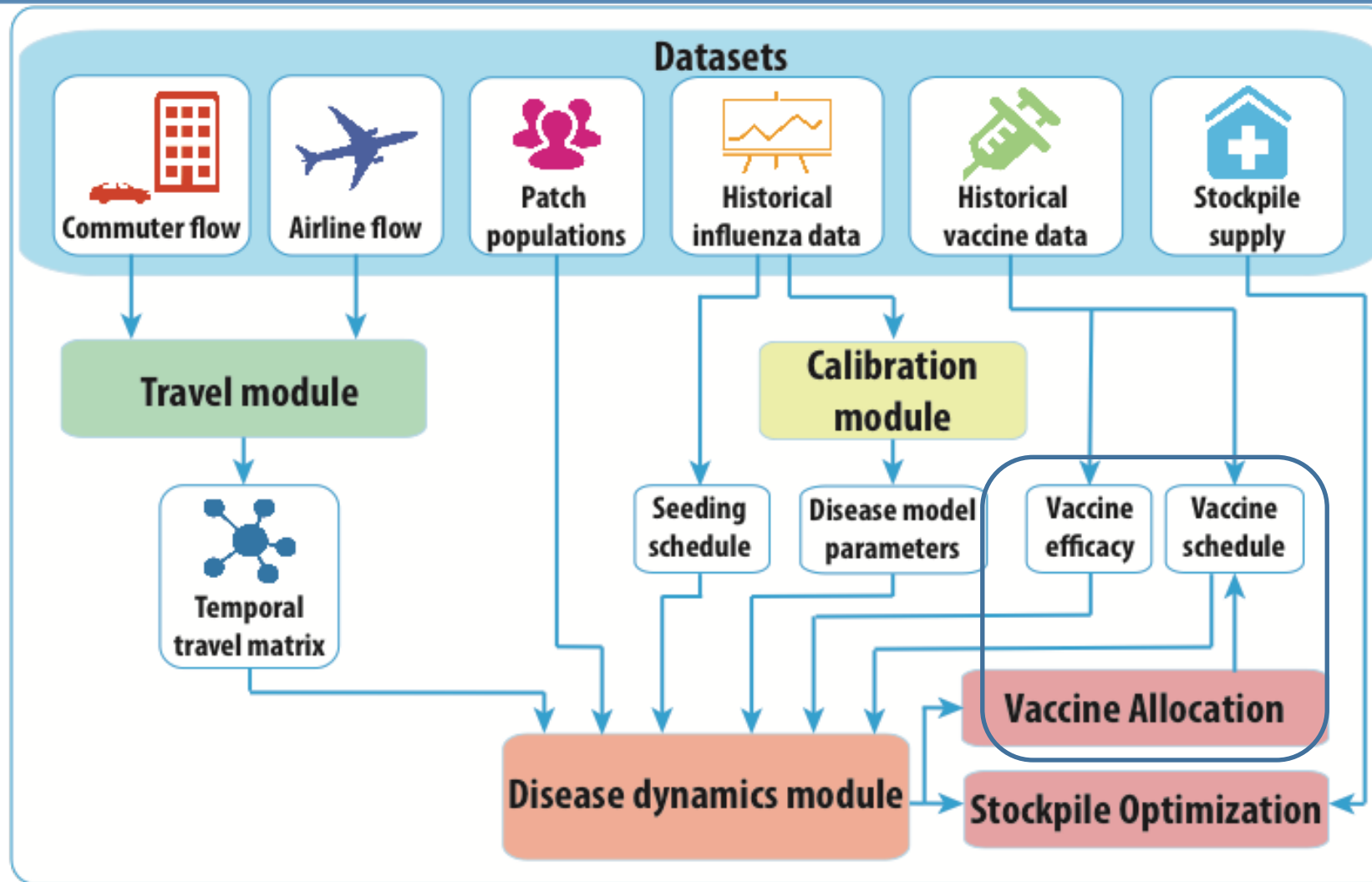


Calibration module

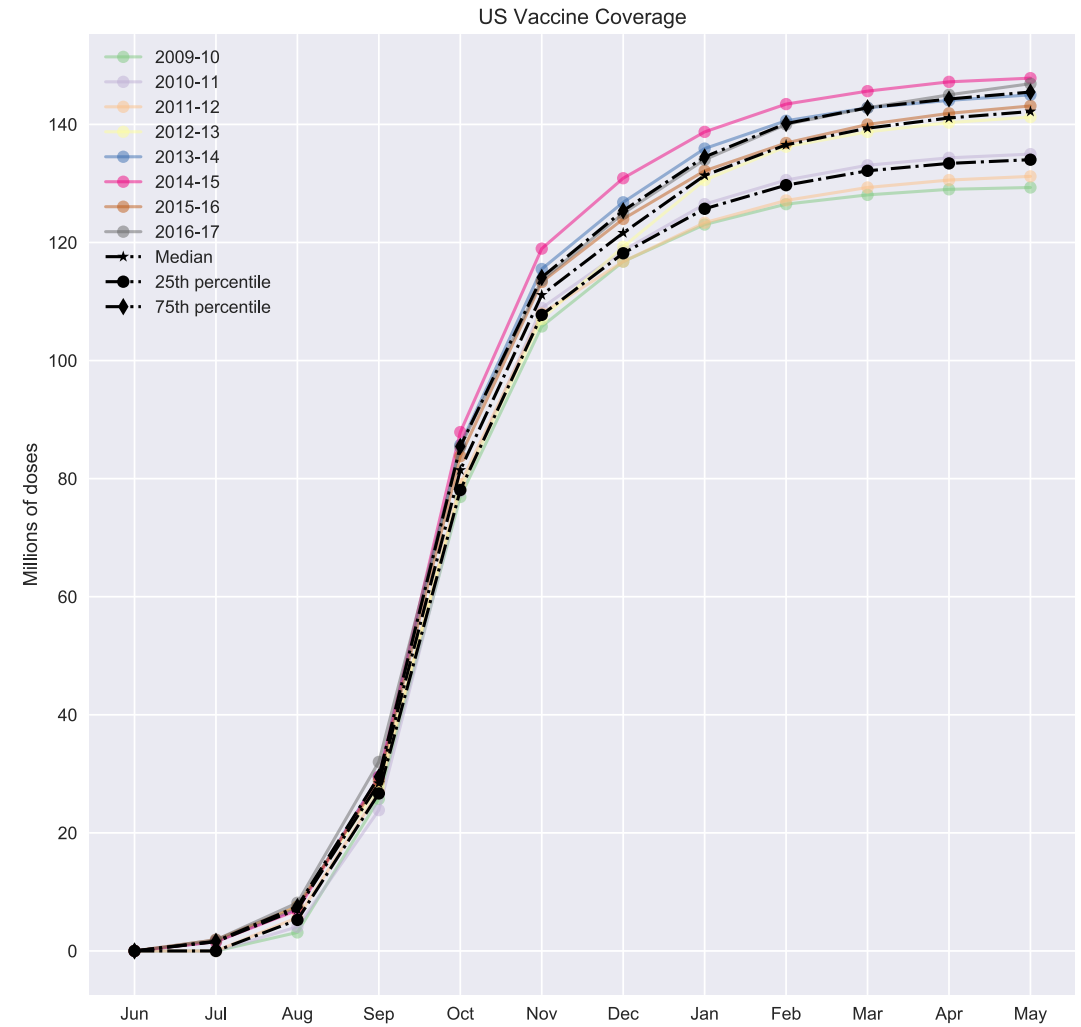
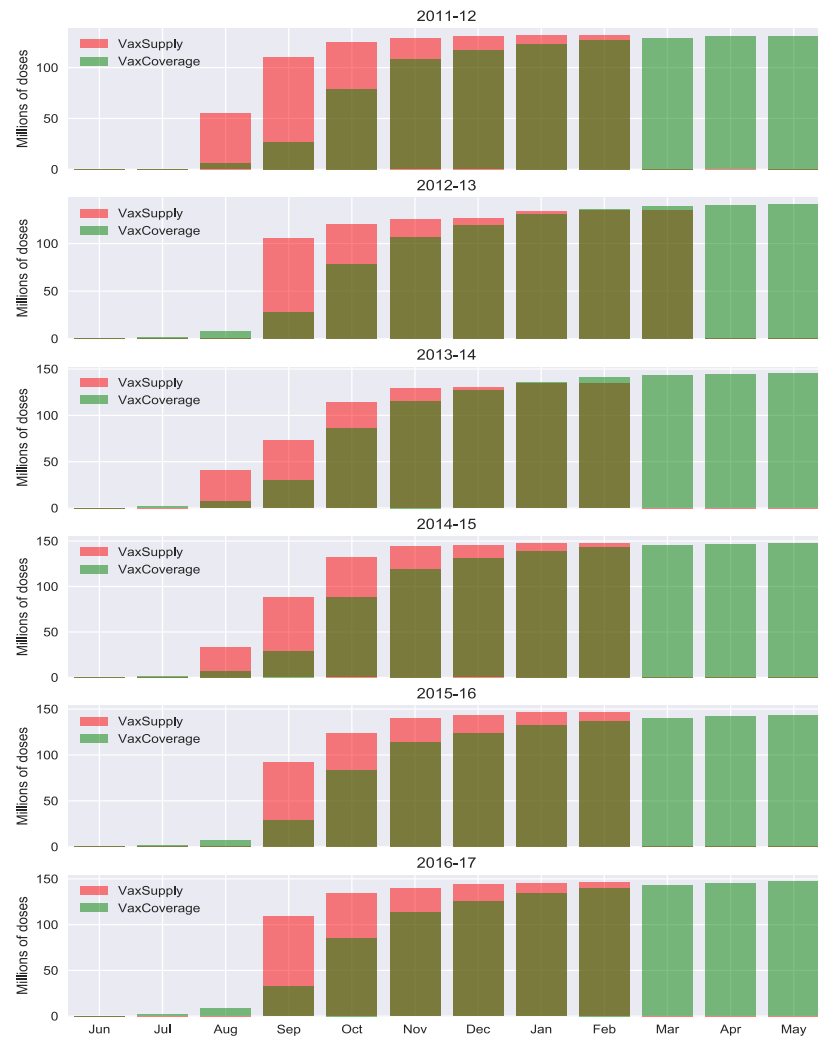
- The process of identifying the right parameters for the model
 - To achieve different total attack sizes
 - To replicate historical influenza seasons
- Latin Hypercube sampling (LHS) over the parameter space
 - Transmissibility, seeding amount & timing, vaccine delay & efficacy, airline stay duration
- Target: HHS region attack sizes
- Gaussian likelihood (equivalent to L2 loss function)



Our approach



Vaccine schedule





Optimization module

- Spatiotemporal allocation of vaccines
 - Space - State level (proportional distribution to counties)
 - Time - Weekly
- Temporal budget constraint
 - Number of vaccine doses available each week
 - Historical data source: FluVaxView¹

$$\begin{aligned} & \underset{X}{\text{minimize}} && f(X) \\ & \text{subject to} && \sum_i X_{i,t} \leq B_t, \text{ for all } t, \end{aligned}$$

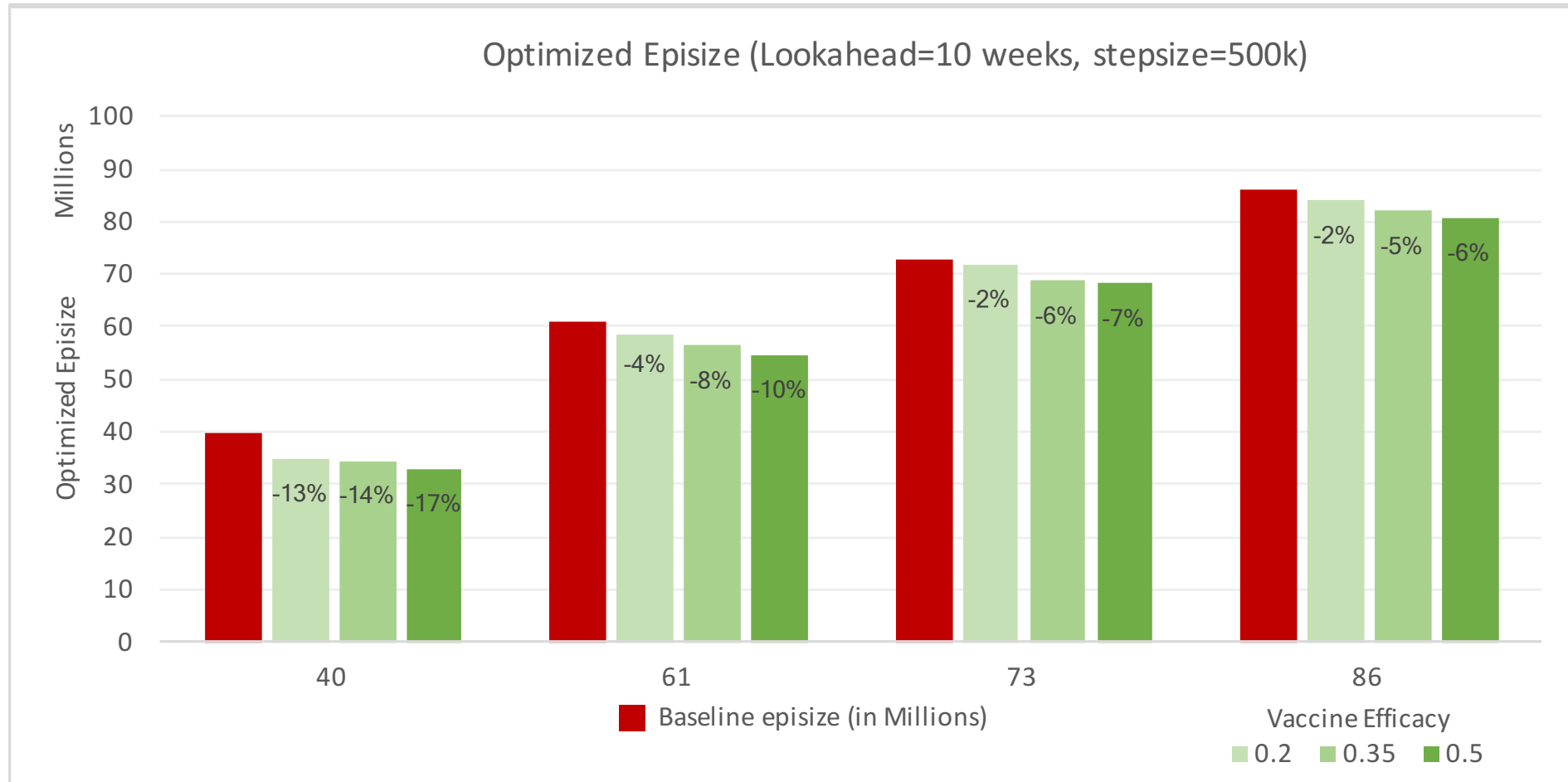
- In our study, objective is to minimize national attack size (total number of infections)

¹ <https://www.cdc.gov/flu/fluview/interactive.htm>

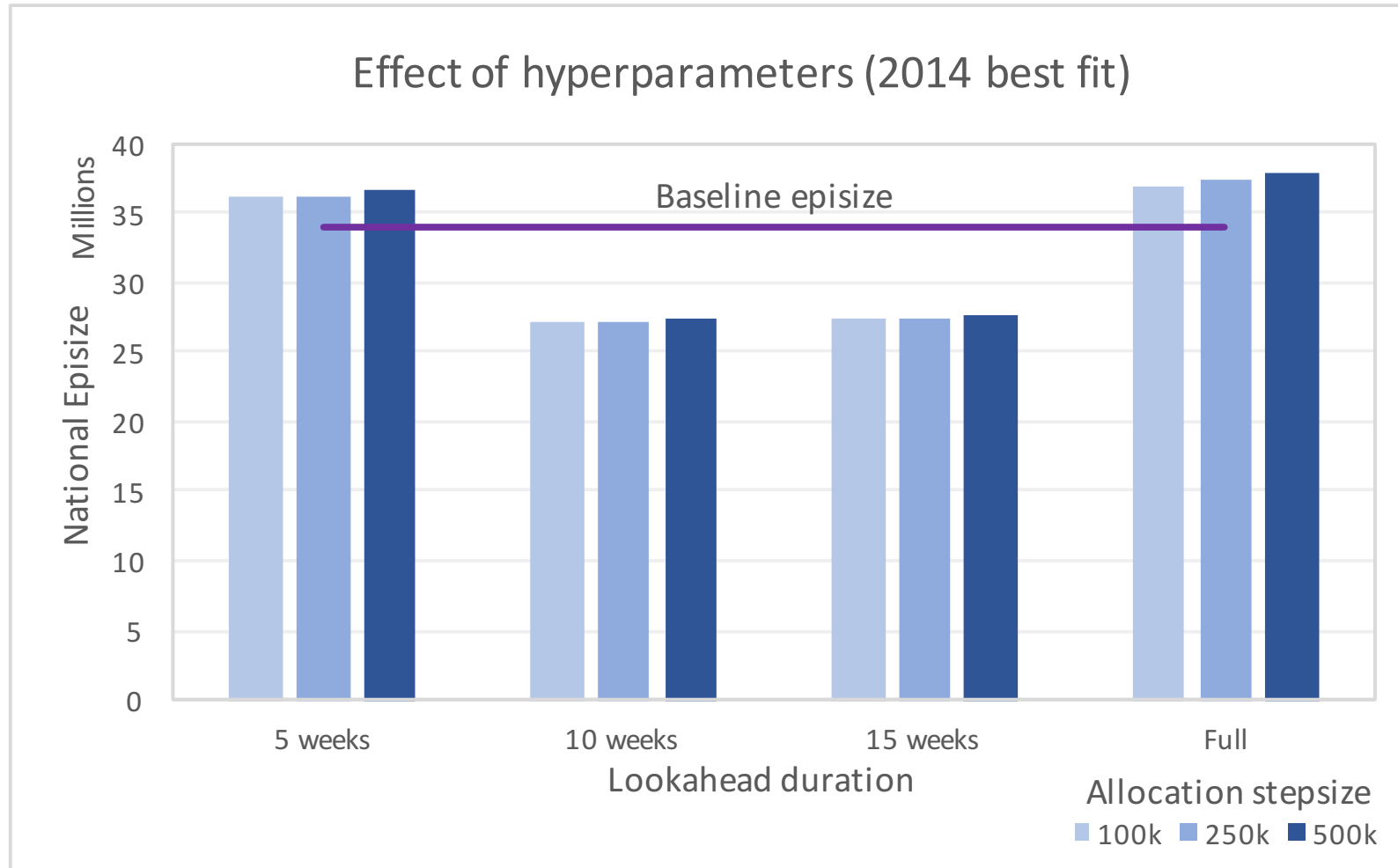
Experiment design

- Four different reference attack sizes (number of infections)
 - 40 million, 61 million, 73 million, 86 million
 - Corresponding to 2014-15, 2009-10, 1957/68 and 1918 estimates
 - Achieved by tuning the transmissibility
- Vaccine efficacy: Low (0.2), Medium (0.35), High (0.5)
- Other parameters:
 - $\alpha = 0.67$ (latent period = 1.5 days), $\gamma = 0.4$ (infection period = 2.5 days)
 - Vaccine delay = 21 days
- Optimization hyperparameters
 - Lookahead duration: 5 weeks, 10 weeks, 15 weeks, Full
 - Vaccine distribution units: 100k, 200k, 500k
- Baseline: Population proportional vaccine allocation

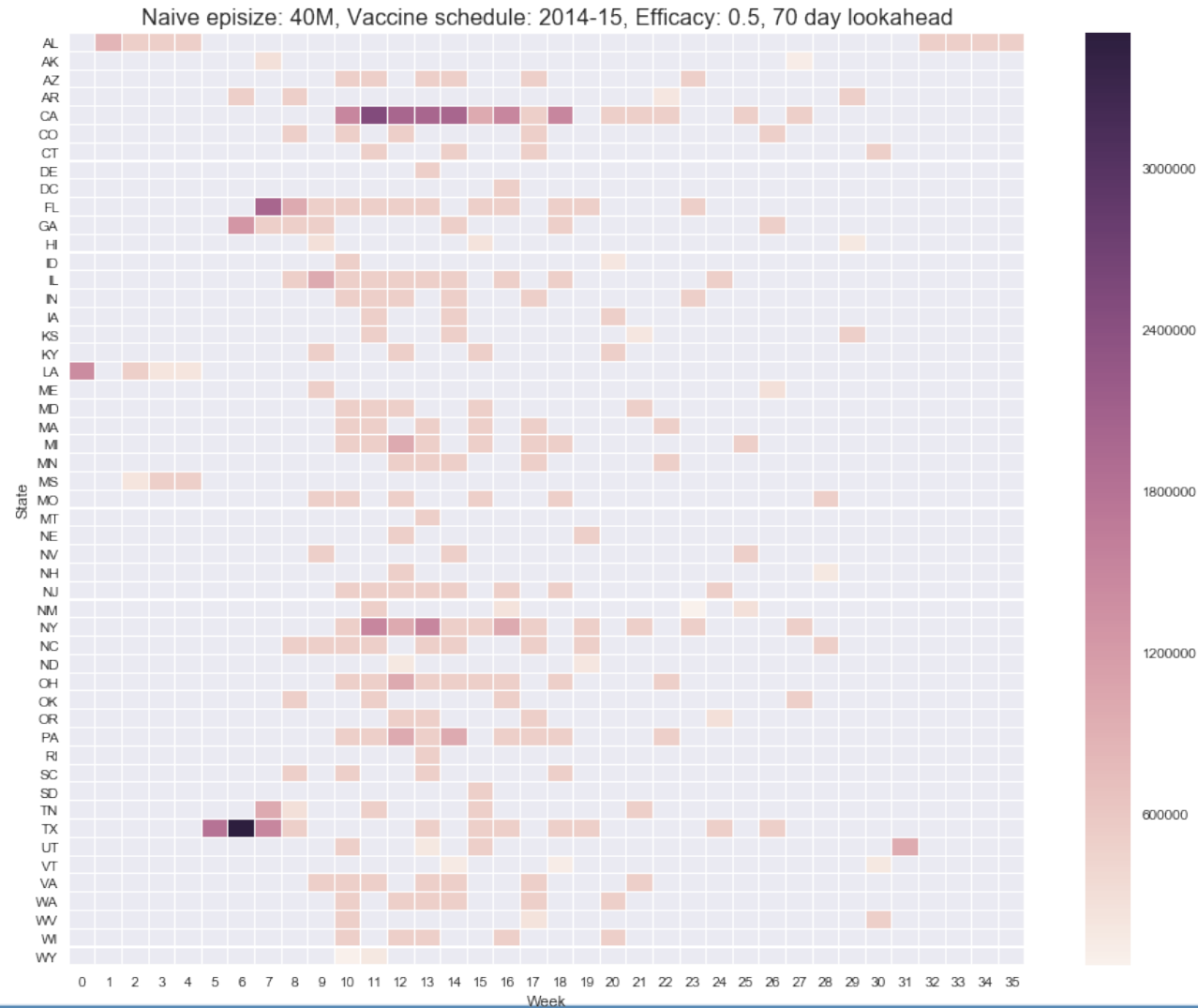
Effect of Optimization



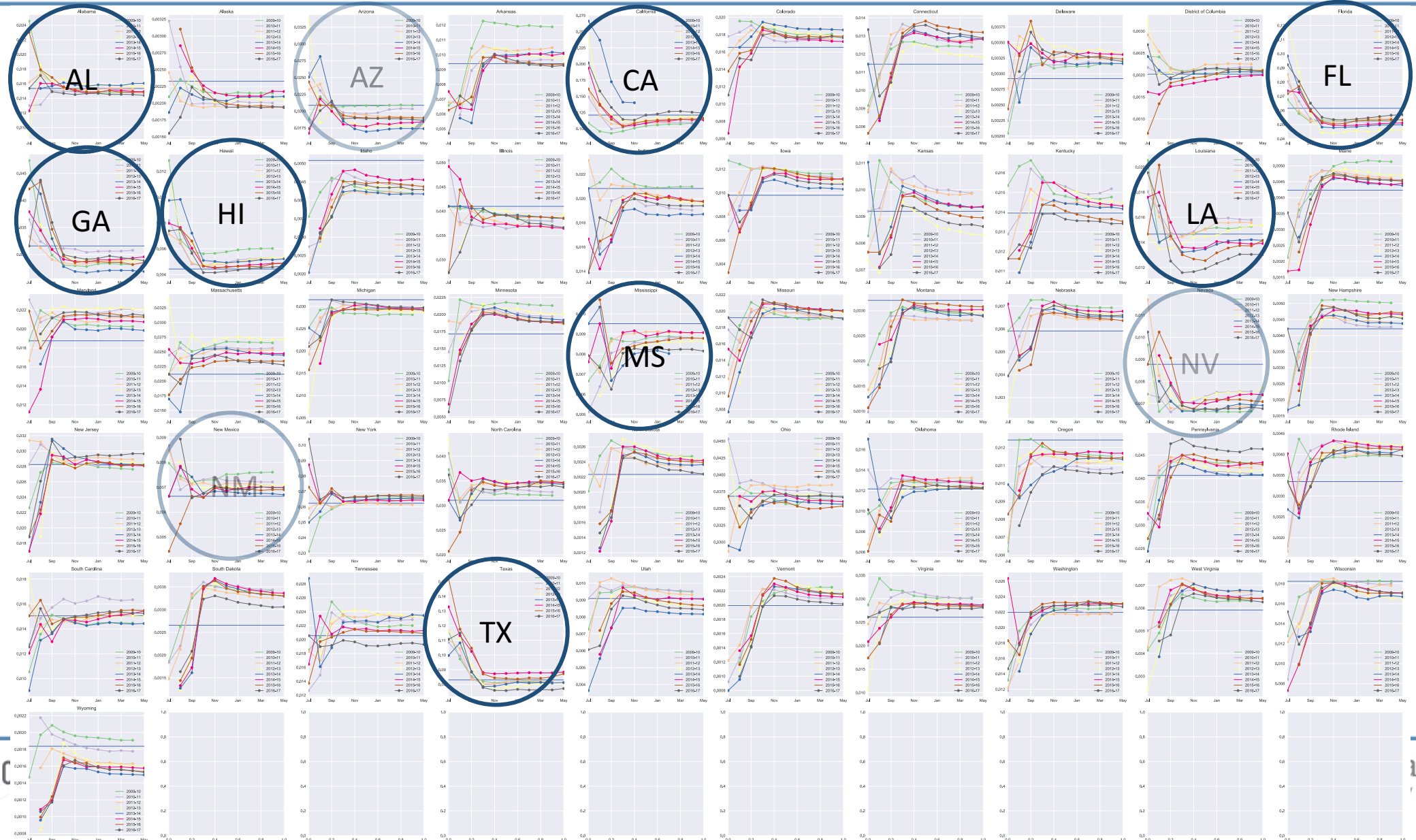
Effect of hyperparameters



Spatio-temporal allocation



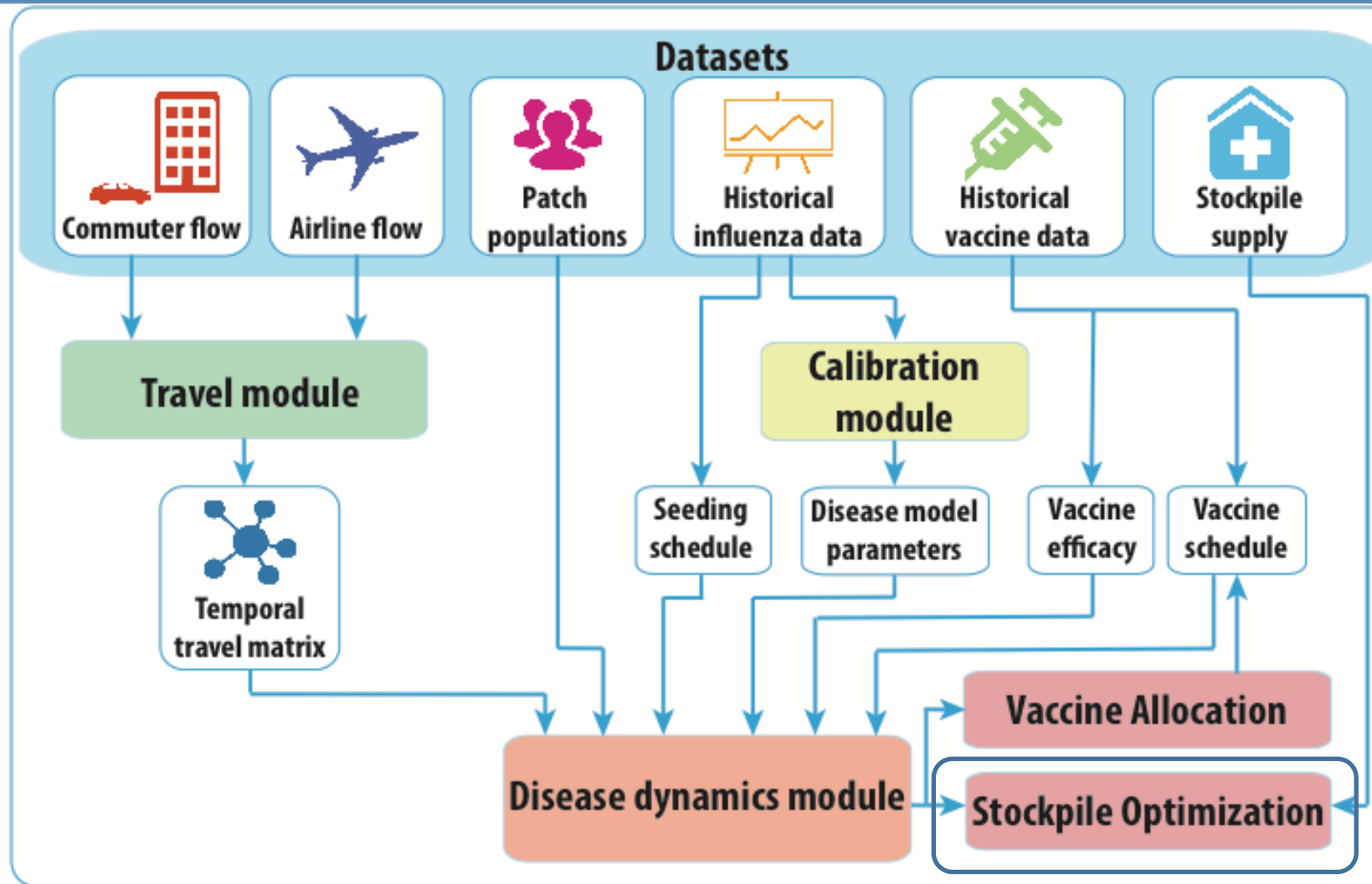
State level coverage



Open questions

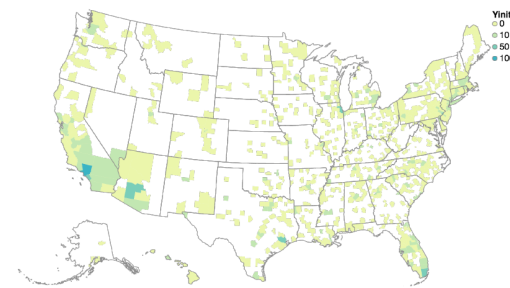
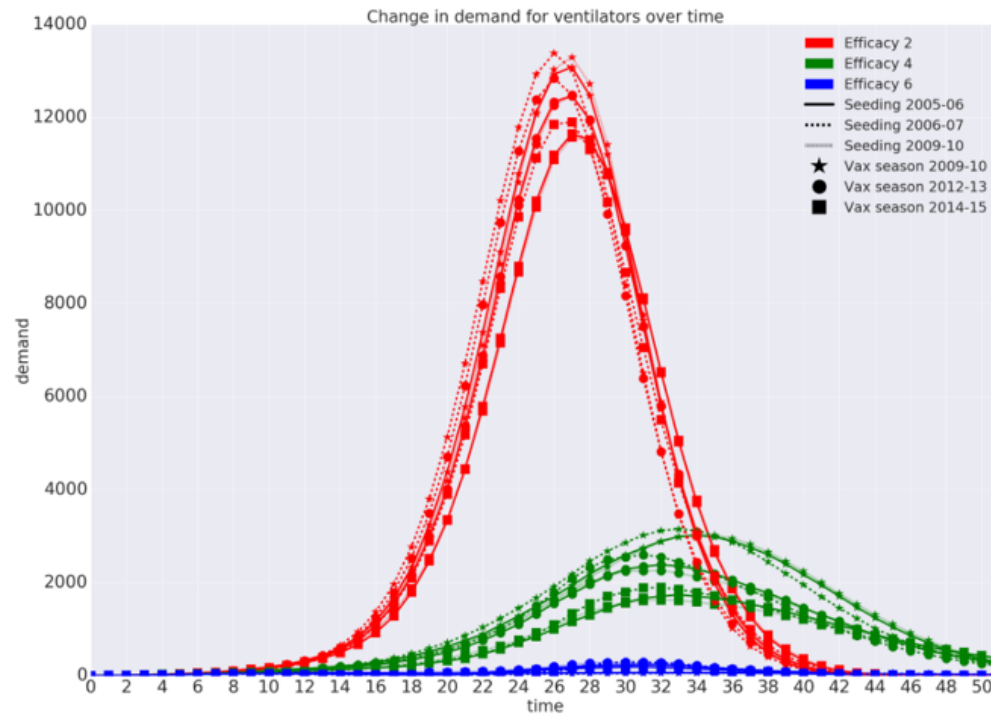
- Is there some form of local optimization already going on?
- Which of the following is true?
 - Higher influenza incidence -> Higher vaccine coverage
 - More observed cases in the neighborhood (decentralized)
 - Historically early states have early vaccine campaigns (centralized)
 - Higher vaccine coverage -> Lower influenza incidence
 - Depends on vaccine efficacy and vaccine delay
- Raises interesting questions on production and supply chain logistics, esp. for pandemic scenarios

Our approach

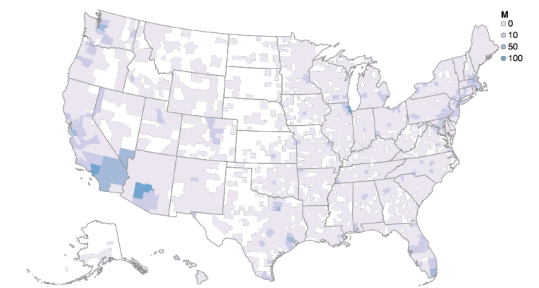


Related: Stockpile optimization

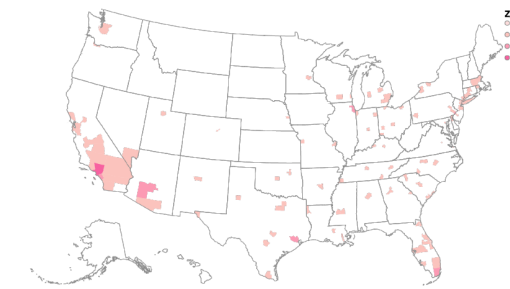
- Spatiotemporal model can be used to estimate hospital demands during pandemic seasons
 - Right-sizing stockpile of ventilators, PPEs, gloves, etc.
 - Optimize local sharing of stockpile



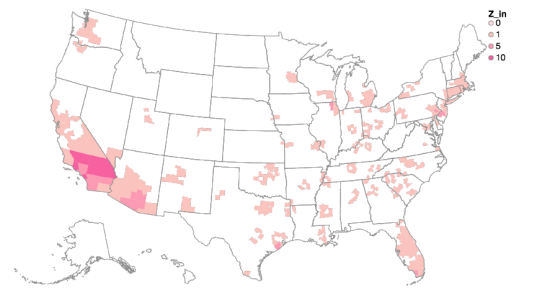
(a) Initial allocation



(b) Average peak deficit



(c) Average maximum out-transfer



(d) Average maximum in-transfer

Figure 5.3: Spatial distribution of allocations, deficits and transfers for a sample scenario ($\mathcal{B} = 6500$, $\theta = 0.9$, $\Delta = 1$, $\alpha = 0.1$)

Limitations & Future work

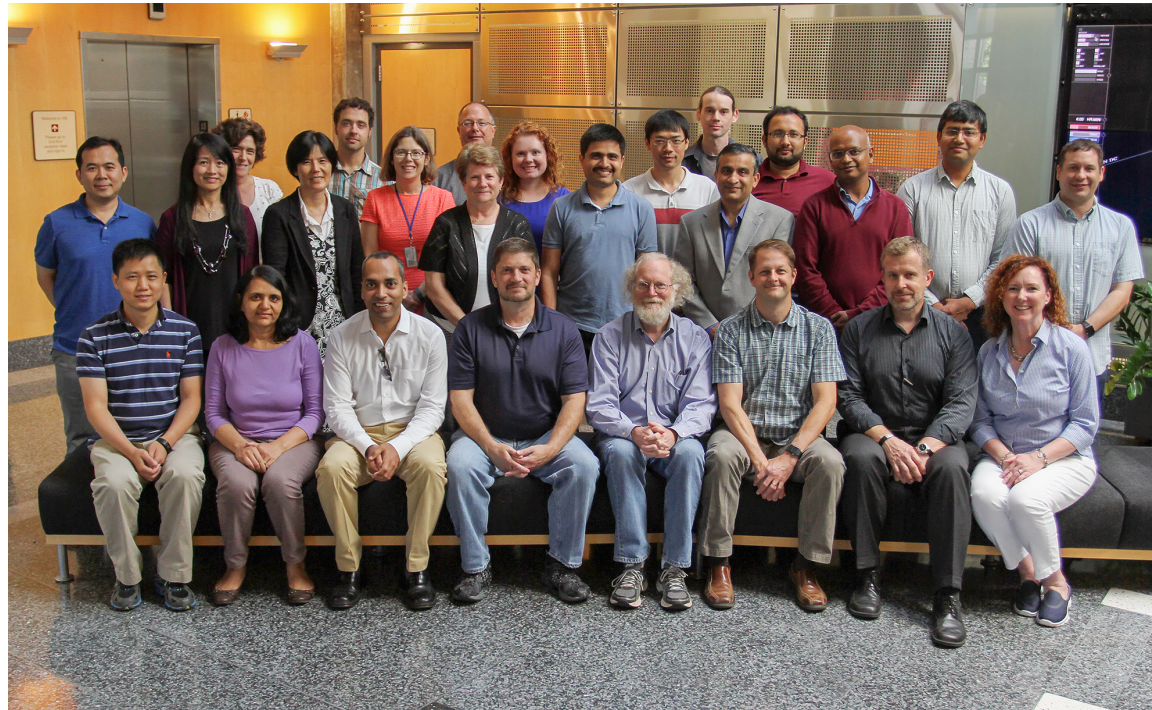
- Incorporate age distribution into the disease model
- Accounting for weather (temperature, absolute humidity)
- More realistic travel model
 - Account for weekends, major holidays, events, vacations, etc.
- Better spatial calibration of historical influenza seasons
- Incorporate compliance behavior for vaccine adoption
 - Optimization goes beyond flu shots (vaccine campaigns, flu clinics, etc.)
- Fairness in distribution? (better objective functions)
- Continued participation in CDC Flu Forecasting Challenge to improve forecasting models

Conclusions

- We have developed a simulation based approach to optimize vaccine allocation for seasonal influenza
- The simulation model accounts for both short-range and long-range mobility across United States
- Results of optimization reveal the importance of spatiotemporal prioritization in vaccine allocation
- Improved models with historical calibration can lead to playbook style approach for vaccine allocation in the future

Acknowledgments

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DTRA CNIMS Contract HDTRA1-11-D-0016-0001,
NIH MIDAS Grant 5U01GM070694 and
NIH Grant 1R01GM109718





PSA



**KEEP
CALM
AND
GET YOUR
FLU SHOT**

Questions?

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