Sandia National Laboratories

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UNCERTAINTY ANALYSIS OF A COVID-19 MEDICAL RESOURCE MODEL

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NOTE: This is part of a larger team effort that includes Pat Finley, Walt Beyeler, Dan Krofcheck, Chris Frazier, Erin Acquesta, Sean DeRosa, Ann Hammer, and Chad Davis

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OUTLINE

- MODELING APPROACH
- UNCERTAINTY ANALYSIS
- RESULTS (RISK INDICATORS)
- SUMMARY

Detailed Surge Modeling of Medical Resource Demands

Goal

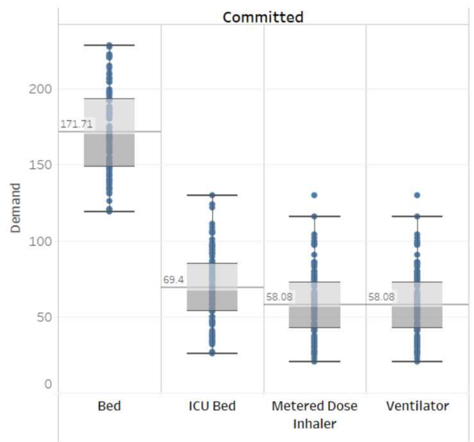
- Calculate resource demands for treating COVID-19 patients based on disease spread projections from epi models
- Anticipate possible times and locations of medical resource shortfalls throughout the pandemic

Approach

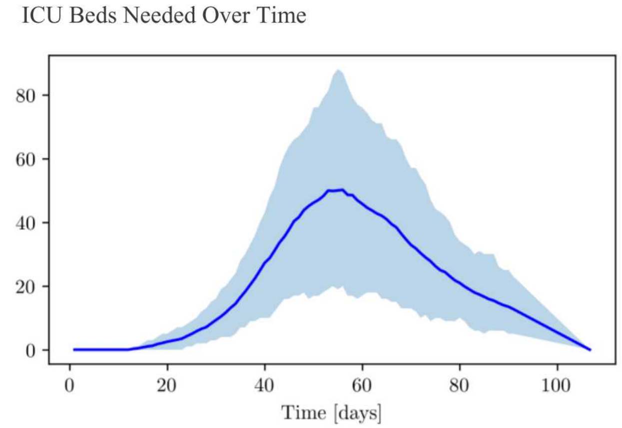
- Use discrete event mathematical model to track patient progress through a hospital treatment system
- Incorporate uncertainty in patient treatment pathways and ranges of resource use per patient to provide risk indicators
- Inputs are patient arrival stream projections from epidemiological models at varying spatial or temporal scales

Results

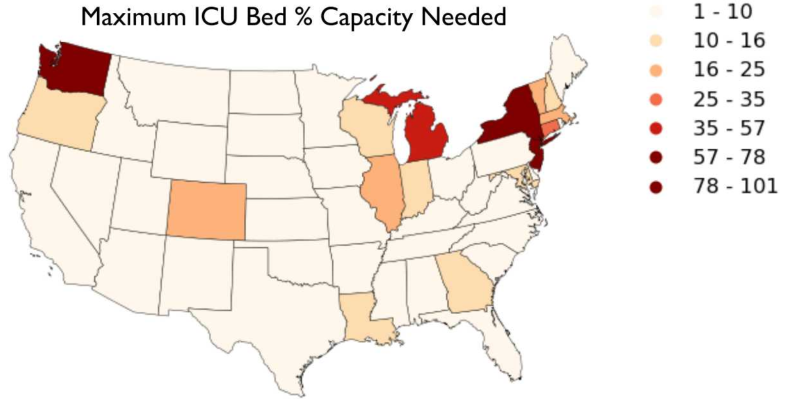
Maximum number of resource needs with a range of uncertainty



Resource needs over time with a range of uncertainty



State or county risk indicators



APPROACH

Inputs

Local

IHME

EpiGrid

Hospital Arrivals Over Time

The approach is agnostic to which epidemiological model is used; we are prepared to receive data from any epi model

Model

Demographics

Treatment Stage

Fates

Parameters

Maximum time on ventilator
Maximum time in ICU if not ventilated
Probability of going to ICU
Probability of needing ventilator
Probability of death if ventilated
Probability of death if not ventilated
etc…

Outputs

Practitioner Need Over Time	Committed Resources Need Over Time	Consumable Resources Need Over Time
Floor Nurse	Beds	Gown
ICU Nurse	ICU Beds	N95 Mask
Physician	Metered Dose Inhaler	Face Shield
Respiratory Therapist	Ventilator	Gloves
		Sedatives

This approach can be applied to any geographic scale for which epi results are available

Model Formulation

Treatment Pathways

- Patients take a treatment pathway through the system
- Spend time in *stages* of the system (in a regular or ICU bed, on a ventilator, etc.)
- Each stage requires different levels and types of resource consumption

Configuration Information

- Possible treatment trajectories and probabilities
- Types of resources to track
- How committed, consumable, and practitioner resources are used
- Scalable to hospital, county, state, or national regions

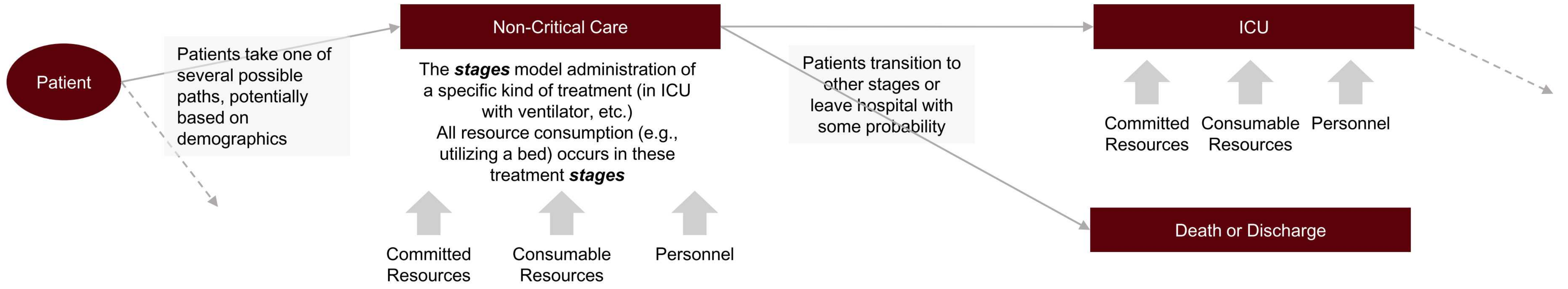
Uncertainty

- Probability that a patient moves to a specific stage
- Time spent in each treatment stage
- Medical providers (how many patients they can treat in a shift, amount of PPE used per patient, etc.)

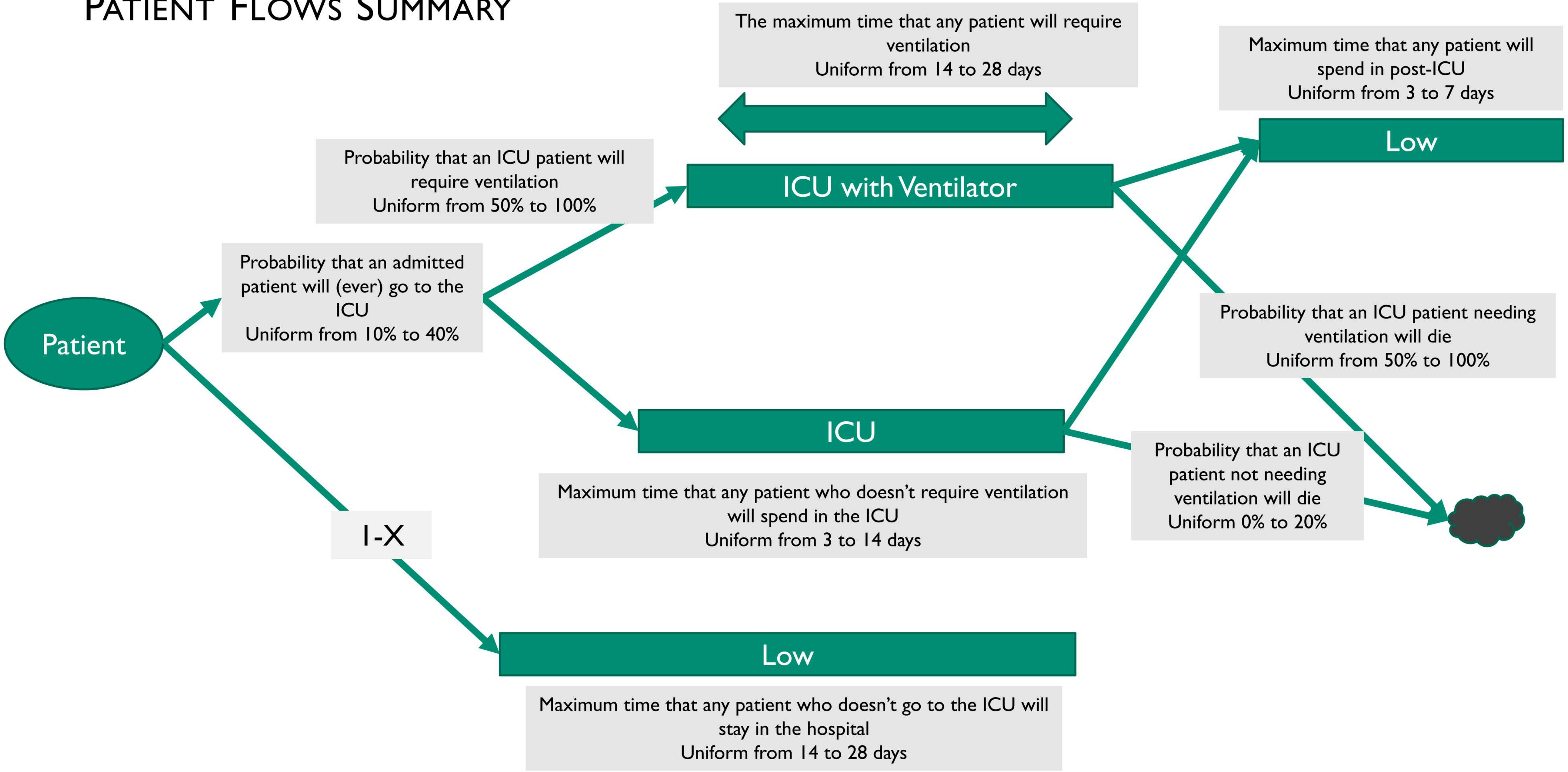
Demographic Information

- Each patient's pathway and fate could be conditional on patient demographics to refine parameter ranges
- This demographic information is not currently available from any epi model, but the model is designed to accommodate these inputs when available

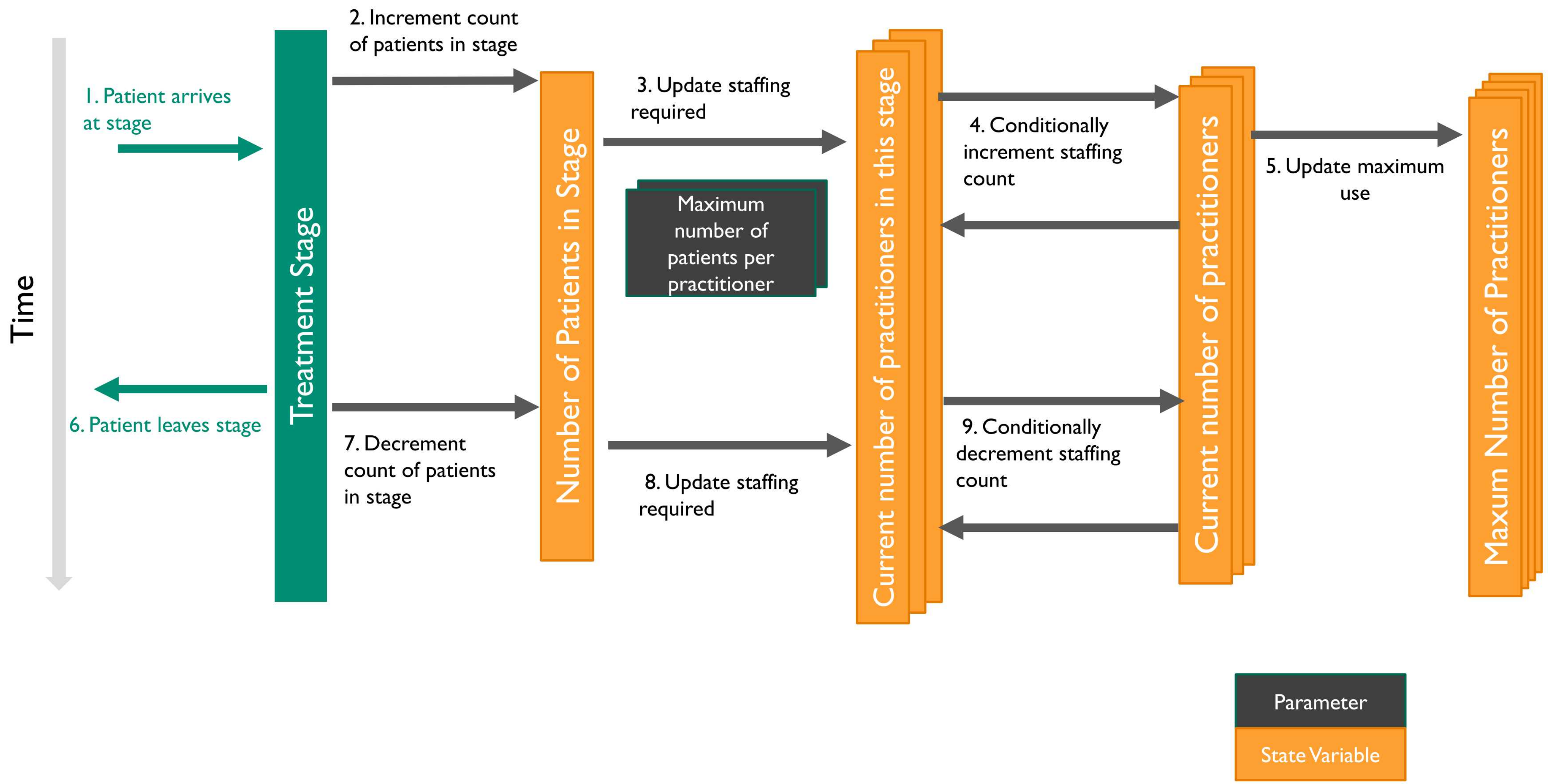
A ***treatment path*** is a specific sequence of ***stages*** for a patient, e.g. non-critical care → ICU care → non-critical care…
Patients follow this path, unless they die are discharged at the end of one of its stages



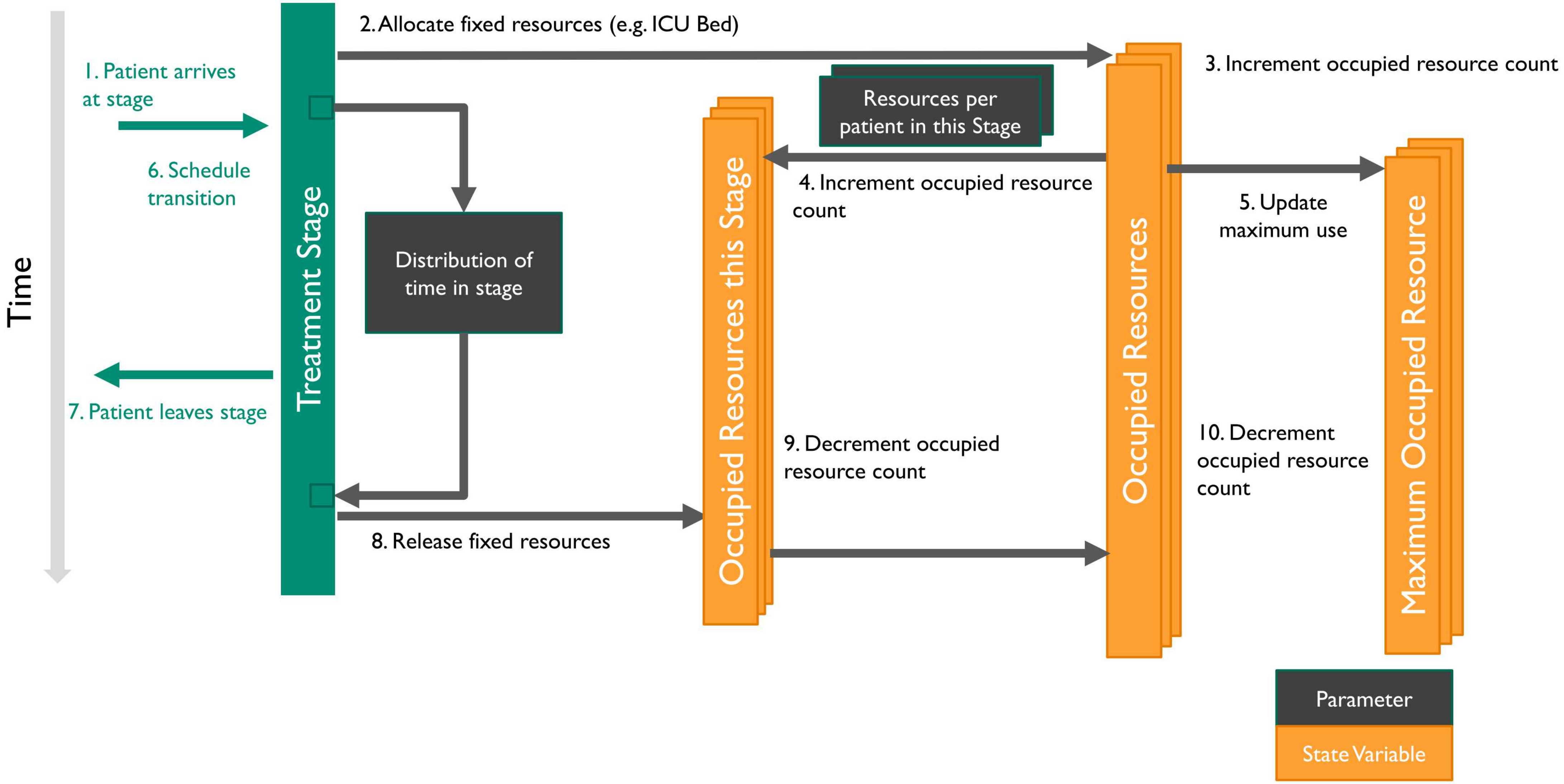
Patient Flows Summary



CALCULATING RESOURCE BURDENS - PRACTITIONERS



CALCULATING RESOURCE BURDENS - COMMITTED



OUTLINE

MODELING APPROACH

UNCERTAINTY ANALYSIS

RESULTS (RISK INDICATORS)

SUMMARY

TERMINOLOGY

Sensitivity Analysis

- Identify most important variables and their interactions
- Understand code output variations as input factors vary
- Often correlation coefficients, scatterplots, or variance-based indices

Uncertainty Quantification

- Determine the probability distribution of code outputs, given uncertainty in input factors
- Assess the likelihood of typical or extreme outputs given input uncertainties: determine mean or median performance, assess variability in model responses, find probability of failure
- Assess how close code predictions are to experimental data (validation) or performance limits (margins)

Calibration

- determine optimal parameter values that yield simulation results which "best match" the experimental data in some sense
- Least-squares methods, Bayesian calibration methods

Verification

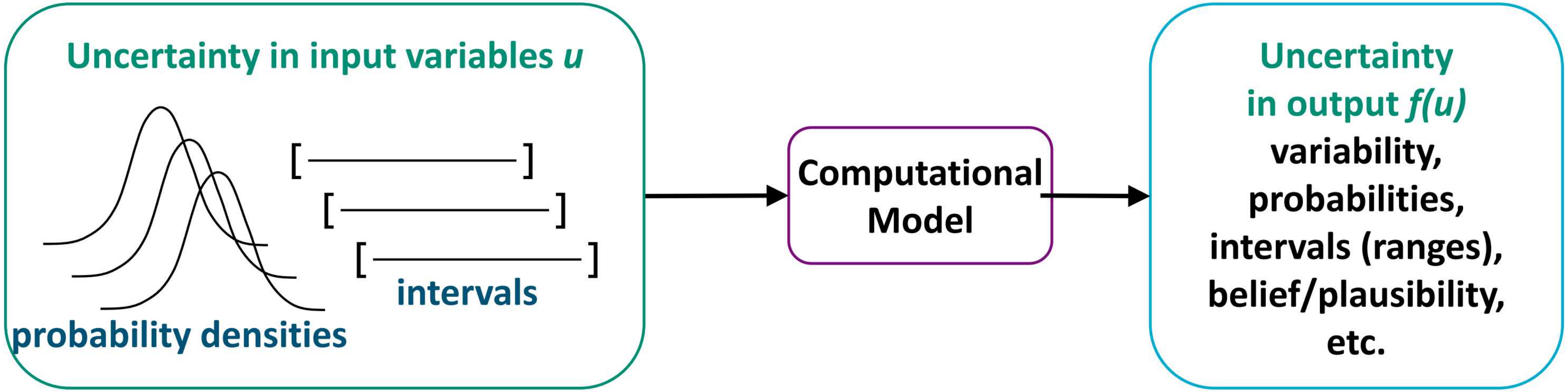
- Are we solving the equations correctly?

Validation

- Is the model adequate for the intended application?

Uncertainty Quantification

UQ methods primarily focus on forward propagation of parametric uncertainties through a model:
determine uncertainty in model output, given uncertainty in input parameters



Example uncertain inputs: physics parameters, material properties boundary/initial conditions, operating conditions, model choice, geometry

Can also perform "inverse UQ" to determine uncertainties in parameters consistent with data

Selecting a UQ Method

Consider variable characterizations and model properties

Sampling (Monte Carlo, LHS)

Robust, understandable, and applicable to most any model

Slow to converge

Moments, PDF/CDF, correlations, min/max

Stochastic Expansions

Surrogate models tailored to UQ for continuous variables

Highly efficient for smooth model responses

Moments, PDF/CDF, Sobol indices

Reliability

Goal-oriented; target particular response or probability levels

Efficient local (require derivatives) / global variants

Moments, PDF/CDF, importance factors

Epistemic

Non-probabilistic methods

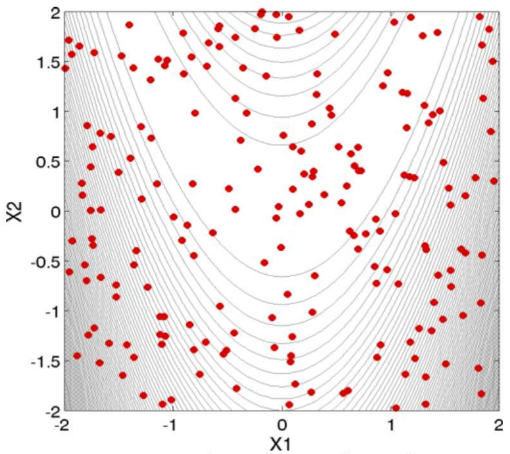
Generally applicable, can be costly when no surrogate

Belief/plausibility, intervals, probability of frequency

Workhorse UQ Method: Monte Carlo Sampling

Sampling methods draw (pseudo-random) realizations from the specified input distributions, run the simulation, and calculate sample statistics:

- Sample moments, min/max, empirical PDF/CDF, based on ensemble of calculations



Monte Carlo sample of two input variables

Robust even for complex, poorly-behaved simulations

Slow, though reliable convergence: $O(N^{-1/2})$, (in theory) independent of dimension

Parallelism: all samples are known at onset and can be evaluated concurrently

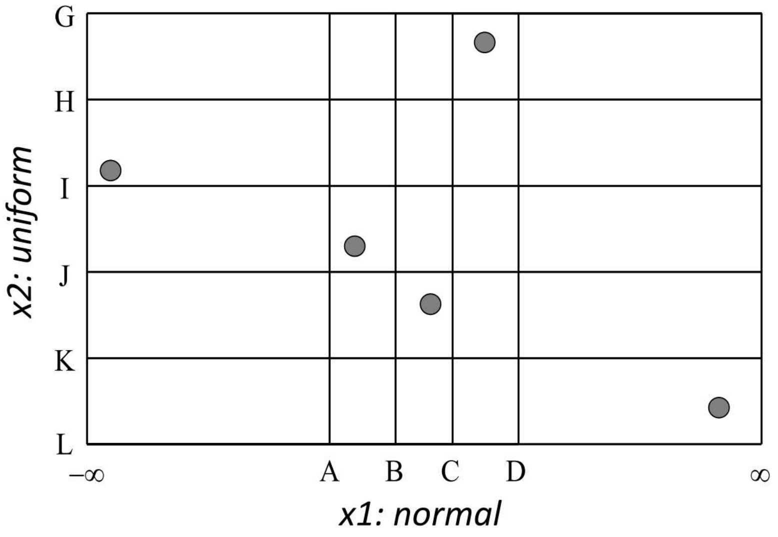
LATIN HYPERCUBE SAMPLING (LHS)

Stratified Sampling method that decomposes the input into equi-probable strata and assigns one sample to each strata

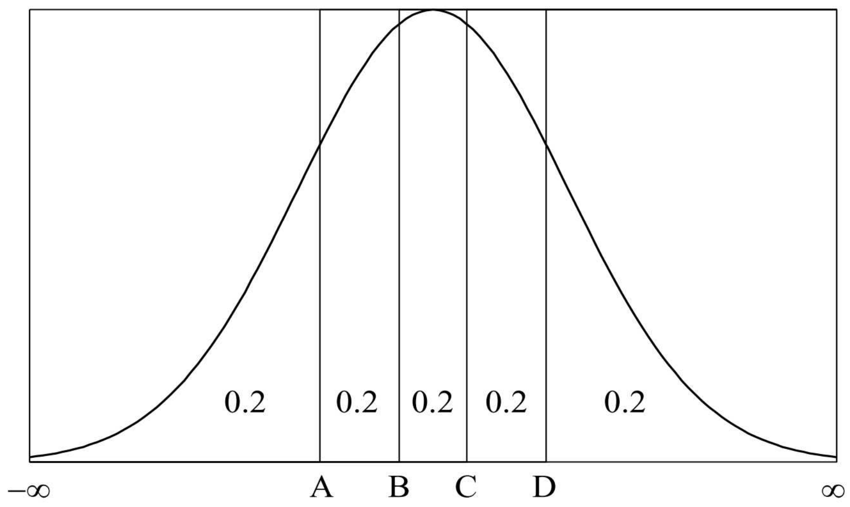
- Developed by Iman (SNL) and McKay et al. (LANL) in late 1970s, heavily used at DOE labs
- LHS requires fewer samples than plain Monte Carlo to achieve the same accuracy in statistics (standard error of the computed mean, for example).
- Better convergence rate and stability across replicates

LHS is recommended when possible

A two-dimensional LHS of size 5

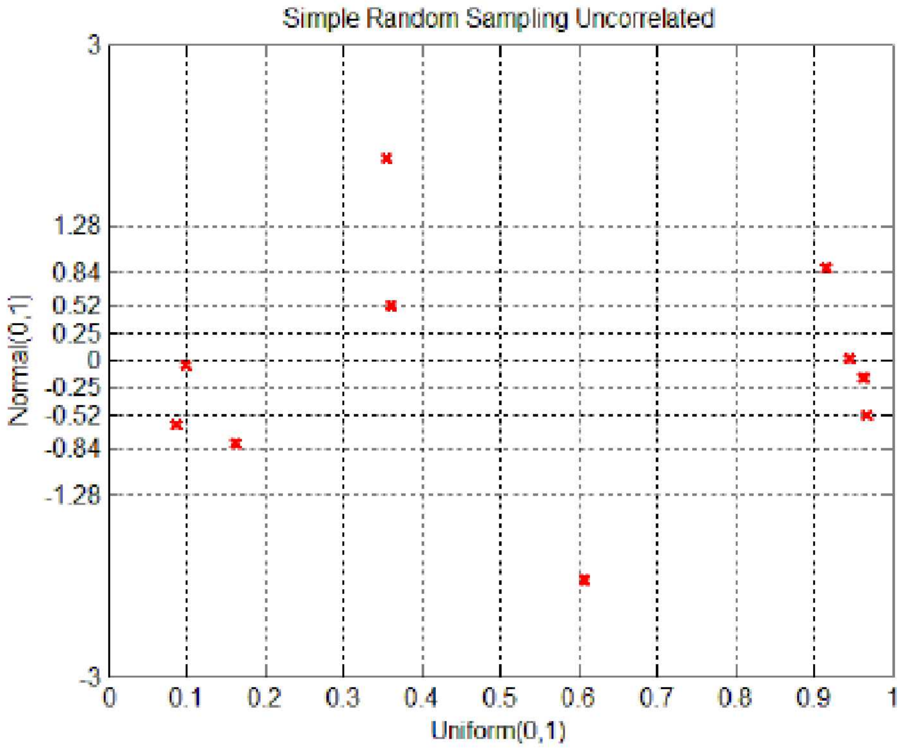


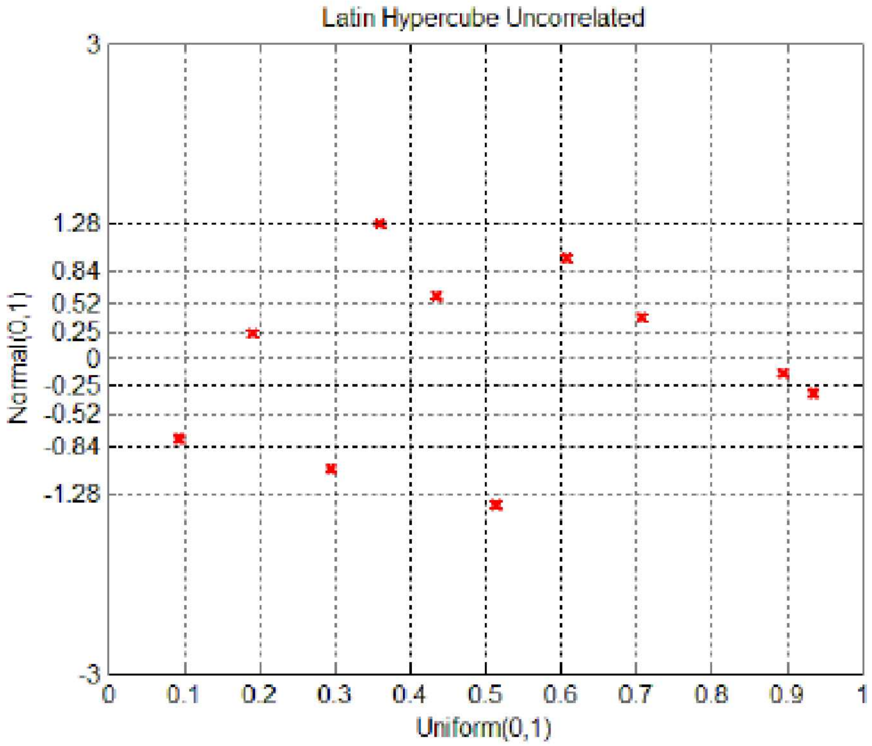
example equi-probable intervals for an LHS of size 5 on a normal random variable



LATIN HYPERCUBE SAMPLING

- Pairing algorithms for multi-dimensional inputs, to pair the samples for one input with samples from the other inputs to honor a specified correlation structure or (most commonly) ensure independent inputs: ONE SAMPLE IN EACH ROW AND COLUMN





STANDARD APPROACH TO GENERATING CORRELATED SAMPLES

Assume there are *p* variables and the user wants to generate *m* samples.

If one has a *p* x *p* target correlation matrix, T, one can generate the *m* x *p* matrix of variables with the desired correlation as follows:

- Take the Cholesky decomposition of T: LL'=T.
- Generate *m* samples of *p* variables assuming independence. We further assume each of the *p* variables is a normal random variable. We can generate an *m* x *p* matrix U of independent variates.
- X=L*U'
- X' is then the sample (of dimension *m* x *p*) with the proper correlation.

- **Assumption: T is symmetric and positive definite**
- **Can modify this approach to induce correlation between the strata using the ranks**

References

Helton J.C. and F.J. Davis. 2003. Latin Hypercube Sampling and the Propagation of Uncertainty in Analyses of Complex Systems. *Reliability Engineering and System Safety* 81:23-69.

Iman R.L. and W.J. Conover. 1980. Small Sample Sensitivity Analysis Techniques for Computer Models, with an Application to Risk Assessment. *Communications in Statistics: Theory and Methods* A9:1749-1842.

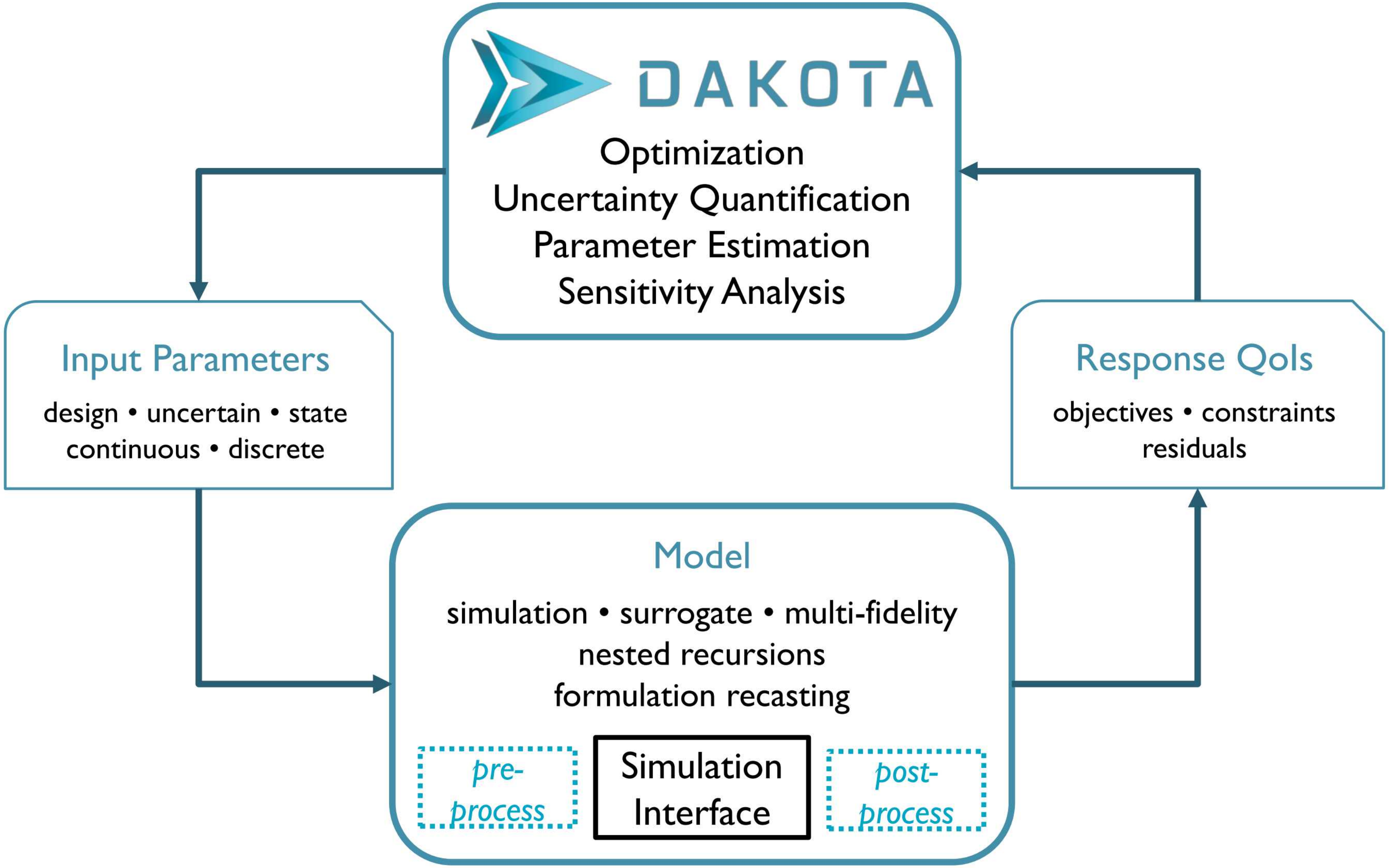
Iman R.L. and W.J. Conover. 1982. A Distribution-Free Approach to Inducing Rank Correlation Among Input Variables. *Communications in Statistics: Simulation and Computation* B11:311-334.

Iman, R.L., Davenport, J.M., and Ziegler, D.K. (1980). "*Latin Hypercube Sampling (Program User's Guide),*" Technical Report SAND79-1473, Sandia National Laboratories, Albuquerque, NM.

Iman, R.L., and Shortencarier, M.J. (1984). "*A Fortran 77 Program and User's Guide for the Generation of Latin Hypercube and Random Samples for Use with Computer Models,*" NUREG/CR-3624, Technical Report SAND83-2365, Sandia National Laboratories, Albuquerque, NM.

Swiler, L. P. and G. D. Wyss (2004). "*A User's Guide to Sandia's Latin Hypercube Sampling Software: LHS Unix Library/Standalone Version.*" Technical Report SAND2004-2439. Sandia National Laboratories, Albuquerque, NM.

Sallaberry C.J., J.C. Helton and S.C. Hora. 2008. Extension of Latin Hypercube Samples with Correlated Variables. *Reliability Engineering and System Safety* 93:1047-1059.



Available at https://dakota.sandia.gov

UNCERTAINTY ANALYSIS OVERVIEW

Goal: Characterize uncertain inputs and propagate them to uncertainty in the resulting resource projections.

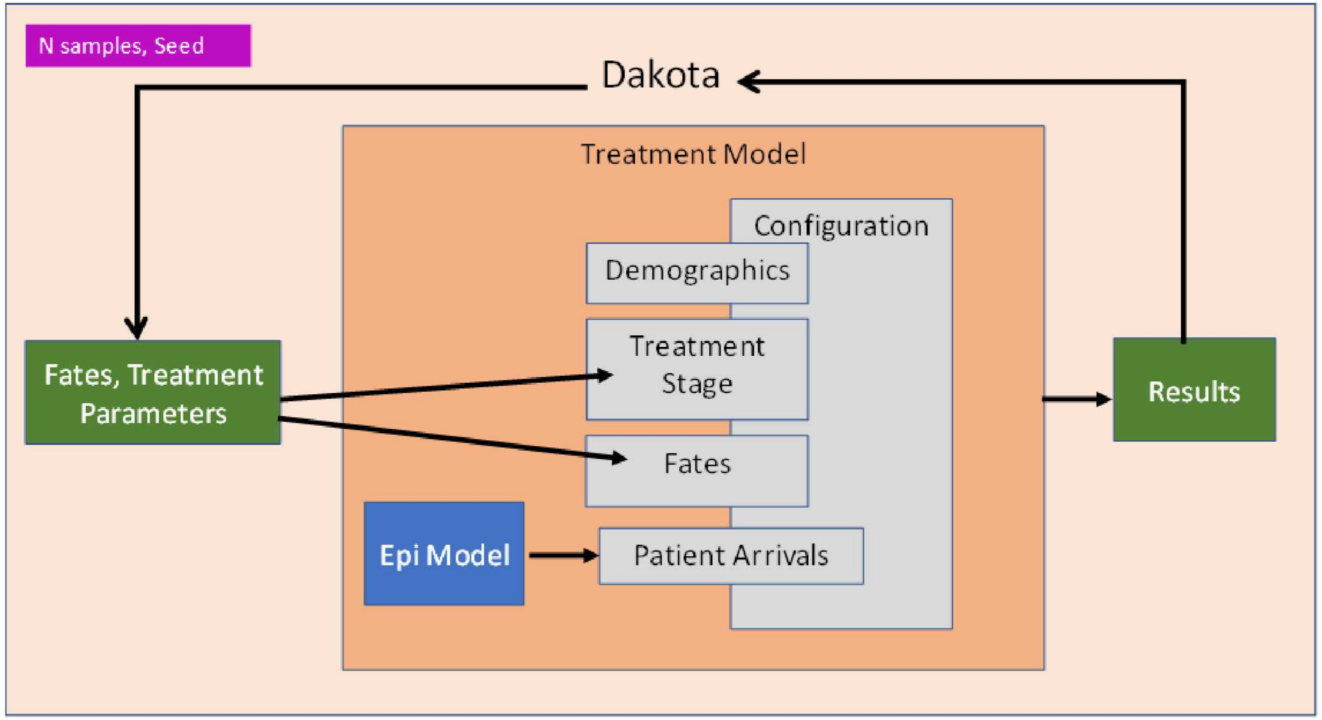
Uncertainties in the model include:

- Probability that a patient moves to a specific stage
- Time spent in each treatment stage
- Medical providers (how many patients they can treat in a shift, amount of PPE used per patient, etc.)

Used Latin Hypercube Sampling (LHS) in Dakota software framework

- 8 continuous parameters
- 18 discrete parameters

Uncertainty quantification process for the resource demand model



Full analysis and documentation is available in Swiler, Portone, and Beyeler, *Uncertainty Analysis of Hospital Resource Demand Model for COVID-19,* Sandia Report, SAND2020-4900, May 2020

3115 COUNTIES * 3 SCENARIOS * 100 SAMPLES OF RESOURCE MODEL

EpiGrid Patient Stream PER COUNTY: Scenario 1

EpiGrid Patient Stream PER COUNTY: Scenario 2

EpiGrid Patient Stream PER COUNTY: Scenario 3

RESOURCE MODEL

Number of resources needed over time

Personnel Resources (Nurses, ICU Nurses, Physicians, Respiratory Therapists)

Fixed Resources (Ventilators, Beds, etc.)

PPE and consumables (Masks, Gown, Gloves, Face Shields, Sedatives)

Postprocessing

- Scripts to aggregate county level data to state level
- Scripts to generate tabular results (statistics on 25 response quantities as a function of time)
- Scripts to generate figures showing uncertainty on resource projections as a function of time

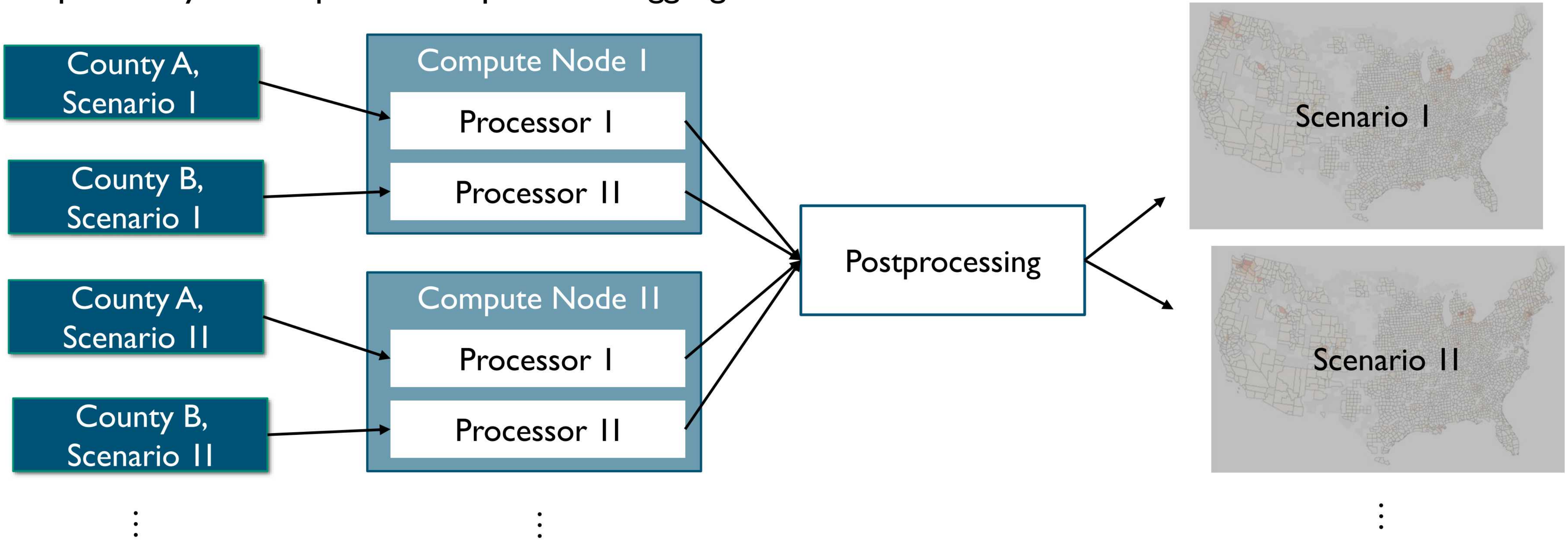
Repeat for 3115 counties →

For each county and each scenario, sample over the uncertain model parameters to generate realizations of time series predictions →

Run scripts for aggregation and generation of results

SCALING UP THE WORKFLOW

- 3115 counties * 3 scenarios * 100 samples of resource model = 934,500 model evaluations
- This would have taken > 500 hours to run on one computer.
- Monte Carlo is embarrassingly parallel - we can sample each county and each scenario independently on a separate computer and aggregate the results at the end.



We were able to do this in < 4.5 hours of computing.

Outline

Modeling Approach

Uncertainty Analysis

Results (Risk Indicators)

Summary

Detailed Analysis for Individual Locations

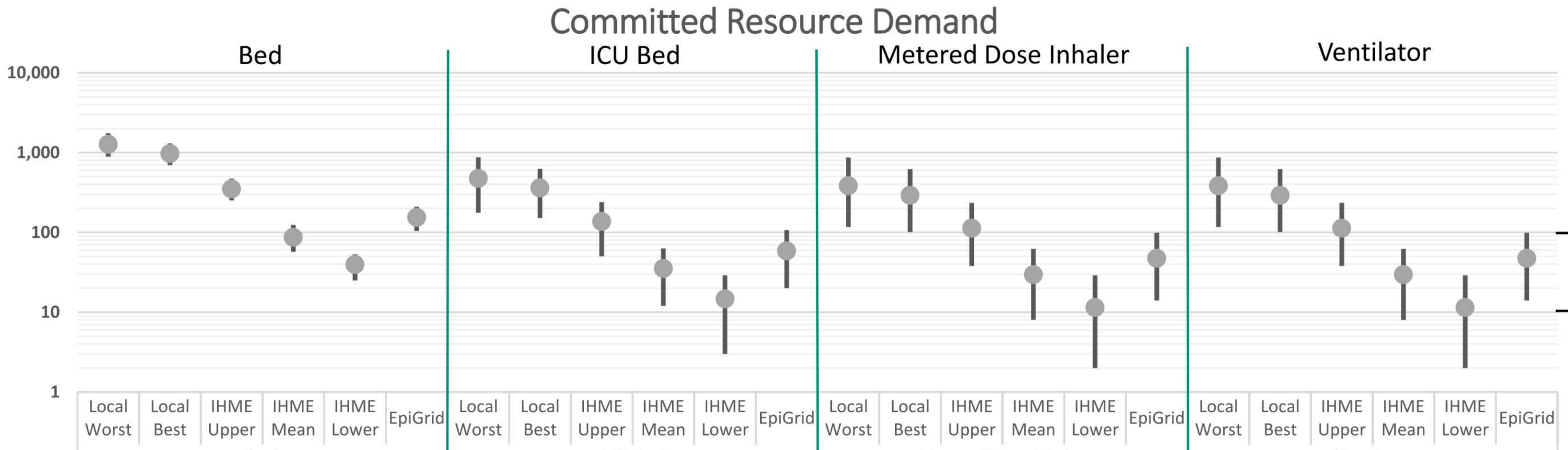
Compare maximum resource demand across different epi models and different scenarios

Inputs

Local | IHME | EpiGrid

Outputs

Committed Resources Need Over Time | Consumable Resources Need Over Time | Practitioner Need Over Time



	Bed						ICU Bed						Metered Dose Inhaler						Ventilator					
	Local Worst	Local Best	IHME Upper	IHME Mean	IHME Lower	EpiGrid	Local Worst	Local Best	IHME Upper	IHME Mean	IHME Lower	EpiGrid	Local Worst	Local Best	IHME Upper	IHME Mean	IHME Lower	EpiGrid	Local Worst	Local Best	IHME Upper	IHME Mean	IHME Lower	EpiGrid
Min	891	699	252	57	25	104	177	151	50	12	3	20	117	101	38	8	2	14	117	101	38	8	2	14
Max	1,749	1,303	472	124	53	210	874	628	240	63	29	107	866	622	235	62	29	99	866	622	235	62	29	99
● Mean	1,269	972	350	87	40	154	476	361	137	35	15	59	384	291	113	30	11	47	384	291	113	30	11	47

Ranges in demand are dictated by uncertainties in parameters (e.g., probability the patient goes into the ICU, needs a ventilator, length of stay)

Detailed Analysis for Individual Locations

Plan for resource needs over time

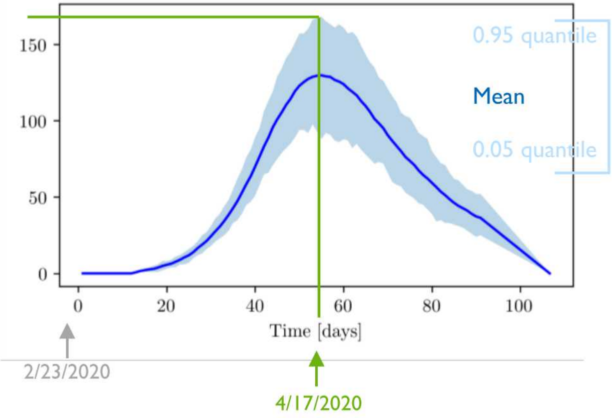
Inputs

Local | IHME | EpiGrid

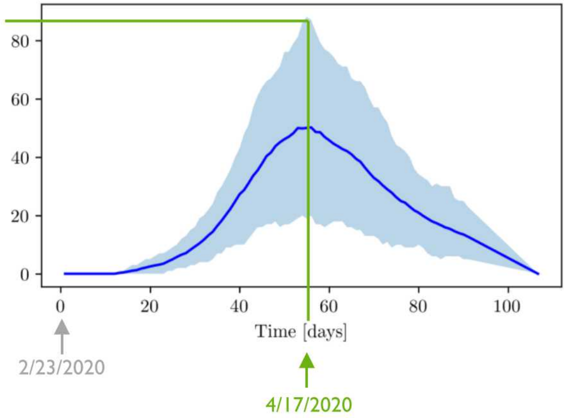
Outputs

Committed Resources Need Over Time | Consumable Resources Need Over Time | Practitioner Need Over Time

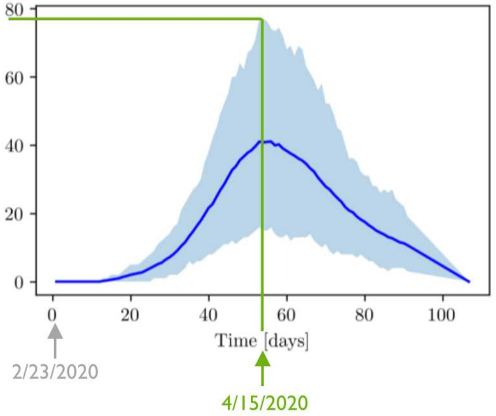
Bed



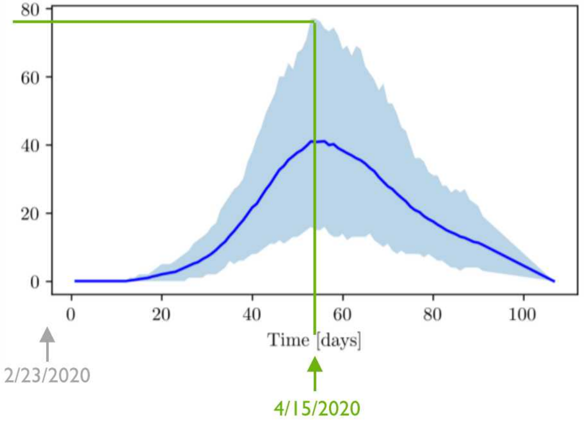
ICU Bed



Metered Dose Inhaler



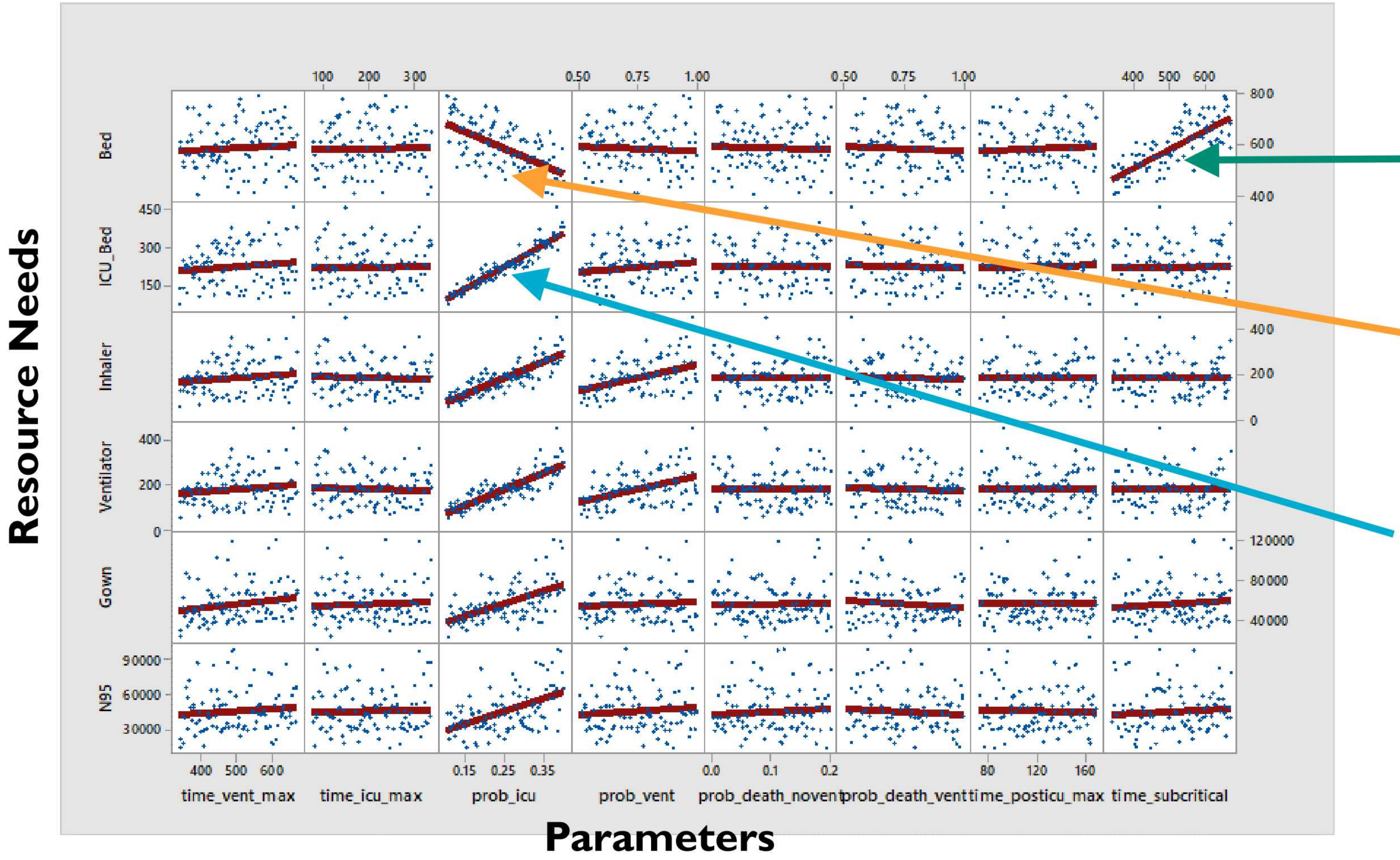
Ventilator



Ranges in demand (illustrated by the light blue quantiles) are dictated by uncertainties in parameters (e.g., probability the patient goes into the ICU, needs a ventilator, length of stay)

Sensitivity Analysis

Goal: Identify most influential parameters

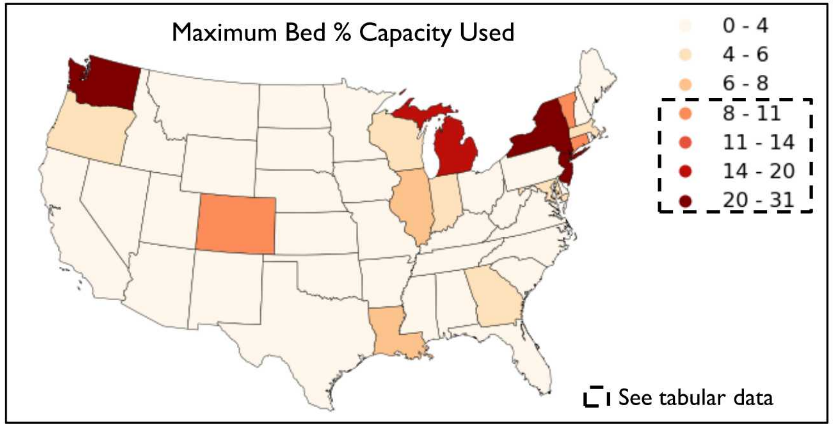


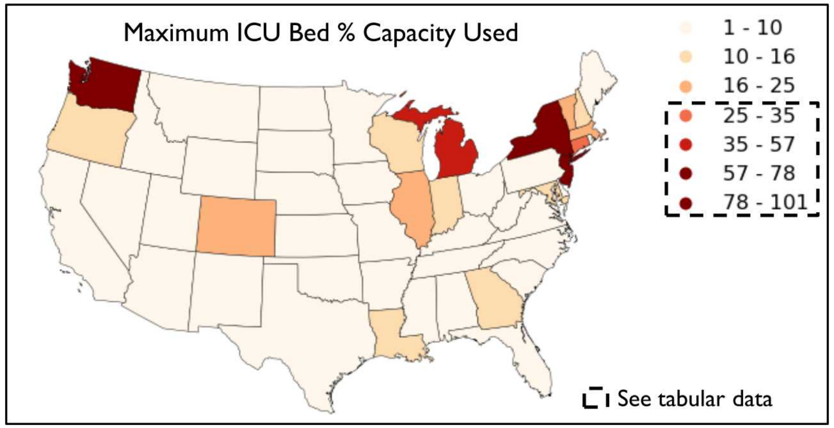
Positive and negative correlations are expected

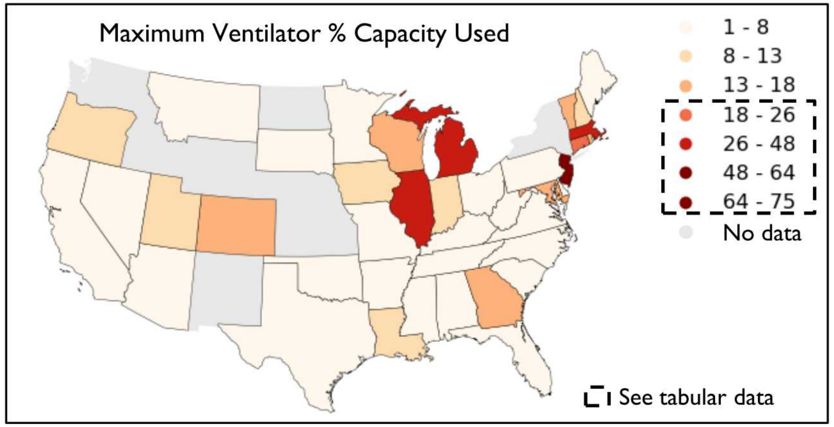
- Maximum time the patient spends in non-ICU care is strongly positively correlated with the number of regular beds needed
- Probability that a patient goes to the ICU is positively correlated with ICU beds needed but negatively correlated with regular beds needed

Probability that a patient goes to the ICU is a strongly influential parameter on resources such as the number of ICU beds

NATIONAL SUMMARY: STATE RESOURCE SUFFICIENCY







States with Resource Utilization >8% Capacity	Maximum Bed % Capacity Used
Washington	41.0
New York	33.4
New Jersey	31.0
Michigan	26.9
Connecticut	14.5
Illinois	13.7
Colorado	12.4
Vermont	11.0
Louisiana	10.4
Indiana	9.3
Wisconsin	8.4
Massachusetts	8.2

States with Resource Utilization > 25% Capacity	Maximum ICU Bed % Capacity Used
New Jersey	100.9
Washington	92.8
New York	92.7
Michigan	77.9
Illinois	34.6
Connecticut	34.5
Vermont	31.6
Colorado	26.7

New Jersey % Capacity for ICU Beds

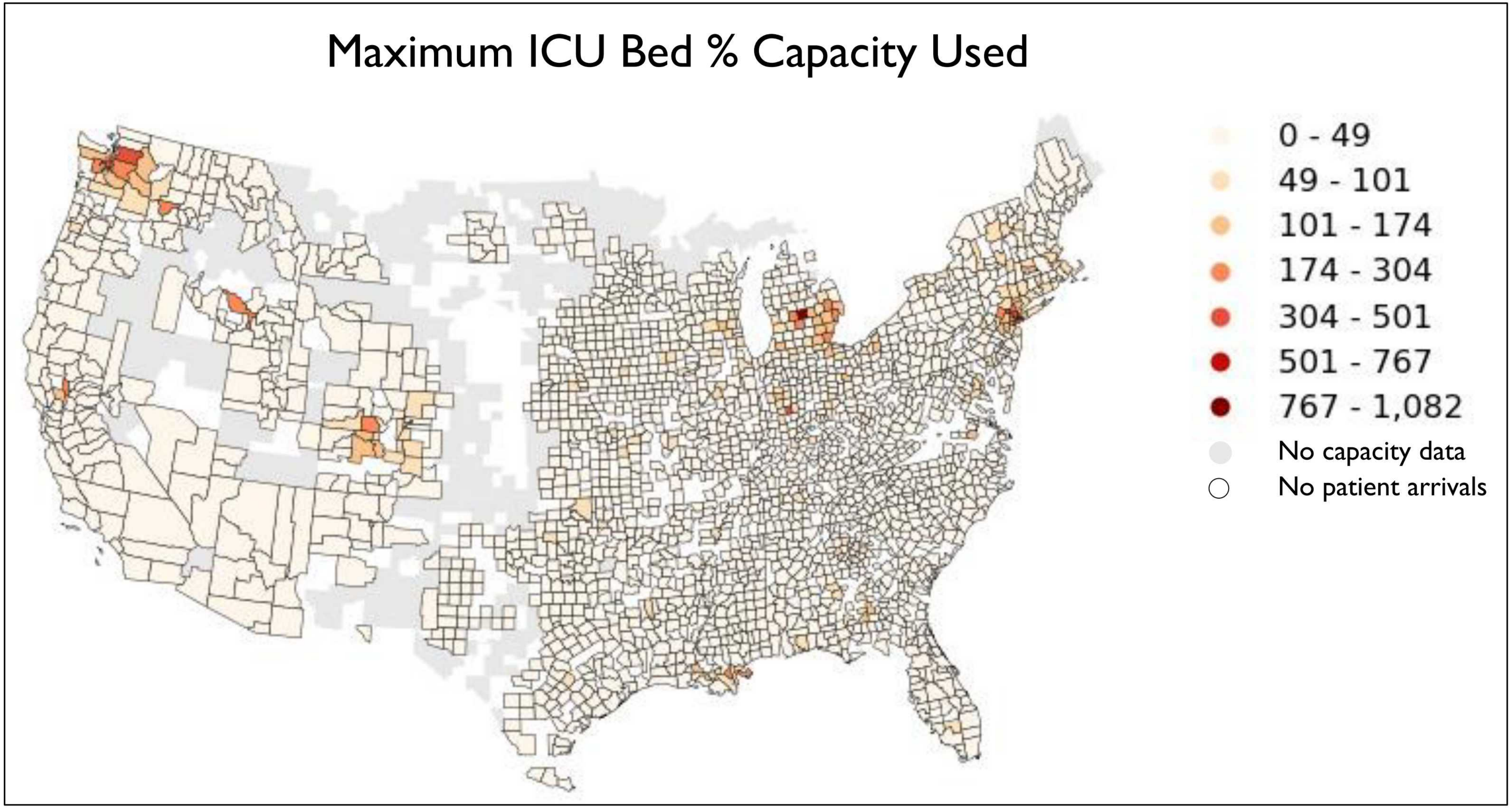
> 100% from 4/17 – 4/25

> 95% from 4/11 – 5/9

States with Resource Utilization >18% Capacity	Maximum Ventilator % Capacity Used
New Jersey	75.0
Michigan	64.3
Illinois	48.1
Massachusetts	42.3
Connecticut	24.5
Rhode Island	23.3
Wisconsin	23.2
Vermont	22.4
Georgia	22.1
Maryland	22.0
Colorado	20.6
Indiana	18.4

Using EpiGrid patient streams, 4/26/2020 dataset, $\beta = 0.3$
Analysis horizon: 3/3/2020 – 7/20/2020

National Summary: County Resource Sufficiency, ICU Beds



County detail provides specificity for state level, and mirrors the same areas of concern.

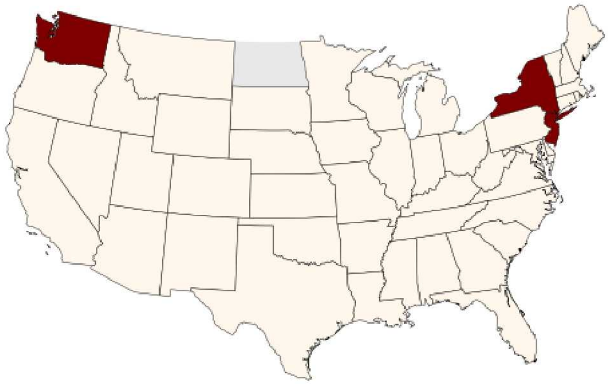
Significant difference in color scale values driven by comparison of county demand to county capacity (vs. state capacity).

Using EpiGrid patient streams, 4/26/2020 dataset, $\beta = 0.3$
Analysis horizon: 3/3/2020 – 7/20/2020

National Summary: Exceedance of Capacity, Social Distancing

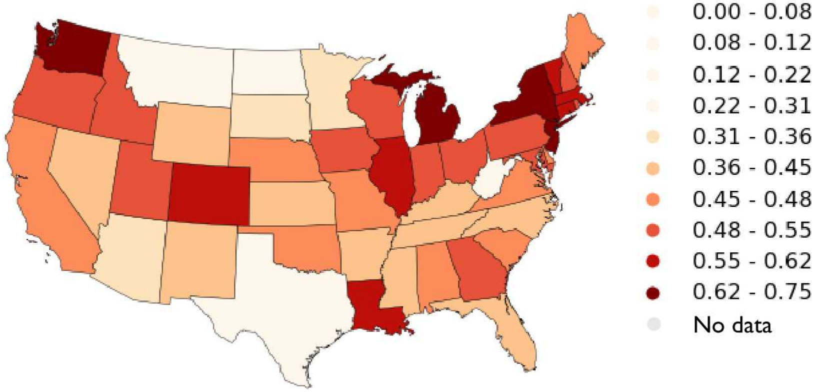
Probability of Exceeding ICU Bed Capacity

Maximum Social Distancing
From 4/11/20 to the end of the simulation, likelihood of infections spreading is discounted 80% relative to doing nothing



Moderate Social Distancing
From 4/11/20 to the end of the simulation, likelihood of infections spreading is discounted 70% relative to doing nothing

Minimal Social Distancing
From 4/11/20 to the end of the simulation, likelihood of infections spreading is discounted 40% relative to doing nothing



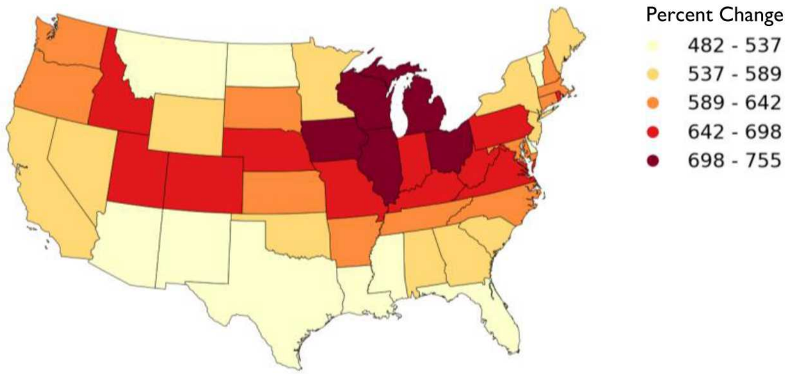
Note that with decreasing degree of social distancing (from left to right in above maps), the probability of exceeding capacity of ICU beds across the country increases significantly.

Using EpiGrid patient streams, 4/26/2020 dataset
Analysis horizon: 3/3/2020 – 7/20/2020

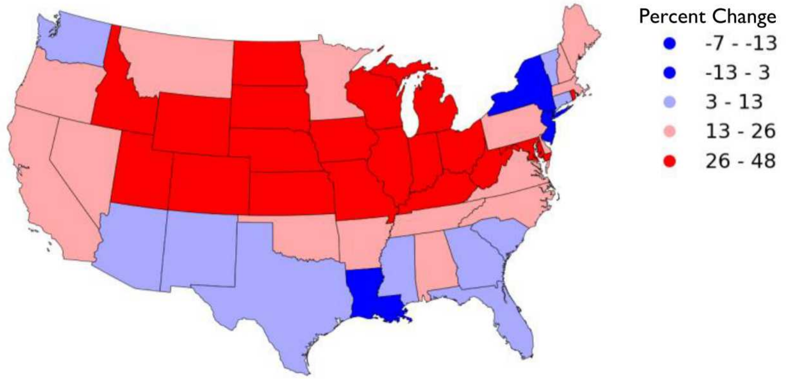
National Summary: Timeseries of Increase/Decrease in Demand

Sequence of maps show increase/decrease of demand from month to month, March – July.
Shading in the "red" family show increases; shading in the "blue" family show decreases.

March to April Change in Bed Demand

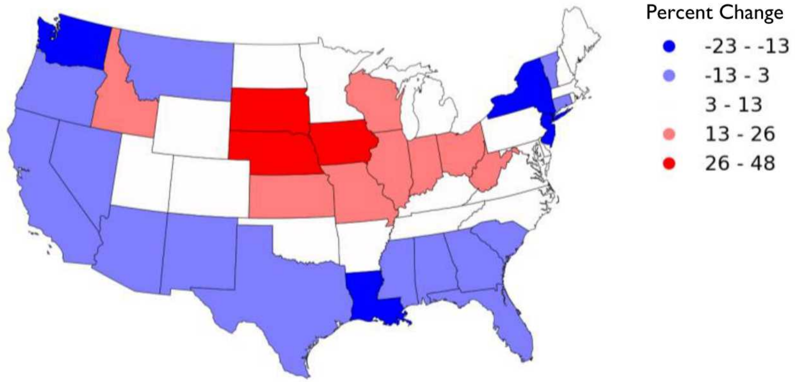


April to May Change in Bed Demand



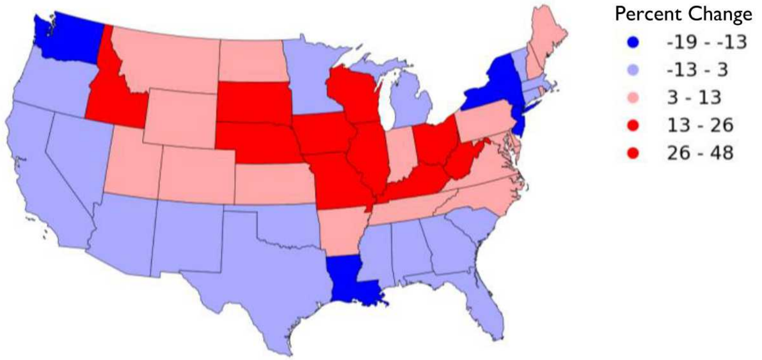
Going into May is the first time some states start to decrease their bed demands

May to June Change in Bed Demand



South Dakota, Nebraska, and Iowa will see the largest percent increases in bed demand

June to July Change in Bed Demand



Idaho and parts of the central U.S. will continue to see increases in bed demand into July

Using EpiGrid patient streams, 4/26/2020 dataset, $\beta = 0.3$
Analysis horizon: 3/3/2020 – 7/20/2020

OUTLINE

MODELING APPROACH

UNCERTAINTY ANALYSIS

RESULTS (RISK INDICATORS)

SUMMARY

SUMMARY

- Performed an uncertainty analysis on a medical resource model to calculate resource needs per state and county across the country
- Used Latin Hypercube Sampling to generate 100 samples within every one of 3145 counties
- Advantages of Sampling:
  - Easy to implement, easy to explain, reproducible
  - Produces unbiased estimates for means, variances and percentiles
  - Preferred when a sufficiently large number of samples are affordable
  - Often used with large discrete input parameter spaces
- Disadvantages: slow convergence rate
- Demonstrated use of the High Performance Computing System to set up a framework so that we can "push" new epi model results in a turnkey fashion to generate new predictions, new uncertainty bounds, and new maps

BACKUP

Model Parameters

Group	Parameter	Range	Source
Treatment paths, probabilities, times	Probability of going to ICU	10% to 40%	Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. doi:10.1056/NEJMoa2002032 Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069. doi:10.1001/jama.2020.1585 Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y
	Probability of needing a ventilator (if in ICU)	50-100%	
	Maximum time any patient would require ventilation	14 to 28 days	
	Maximum time in ICU if not on a ventilator	3 to 14 days	

Staffing		Location	
		ICU	General
Practitioner	ICU Nurse	Uniform 1-2	N/A
	Doctor	Uniform 2-10	Uniform 20-50
	Nurse	N/A	Uniform 4-10
	Respiratory Therapist	Uniform 2-6	N/A

Units used per shift in ICU		Resource			
		Gowns	N95 Mask	Gloves	Face Shield
Practitioner	ICU Nurse	2-4	1-4	4-12	1-4
	Doctor	1-2	1	1-12	1
	Nurse	N/A	N/A	N/A	N/A
	Respiratory Therapist	1-2	1	6-12	1

Units used per shift in General		Resource			
		Gowns	N95 Mask	Gloves	Face Shield
Practitioner	ICU Nurse	N/A	N/A	N/A	N/A
	Doctor	1-2	1	1-12	1
	Nurse	2-3	1-3	3-12	1
	Respiratory Therapist	N/A	N/A	N/A	N/A

Epi inputs drive results more than these parameter values

REFERENCES

Treatment Paths and Outcomes

- Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. doi:10.1056/NEJMoa2002032
- Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. doi:10.1001/jama.2020.1585
- Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y.
- Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020 - CDC
- Clinical Characteristics of Coronavirus Disease 2019 in China; Wei-jie Guan, Ph.D., Zheng-yi Ni, M.D., et al. doi: 10.1056/NEJMoa2002032; 10.1056/NEJMoa2002032; New England Journal of Medicine; Massachusetts Medical Society; 0028-4793; UR - https://doi.org/10.1056/NEJMoa2002032;2020/04/04
- Preliminary Analysis of case data from Canada and New Mexico

Usage Rates

- Planning estimates provided by a local New Mexico health service
- Preliminary Analysis of hospital usage and staffing reports provided by NMHA
- CDC guidance cited in: Potential Demand for Respirators and Surgical Masks During a Hypothetical Influenza Pandemic in the United States; Cristina Carias, Gabriel Rainisch, Manjunath Shankar, Bishwa B. Adhikari, David L. Swerdlow, William A. Bower, Satish K. Pillai, Martin I. Meltzer, and Lisa M. Koonin

REPLICATE ANALYSIS

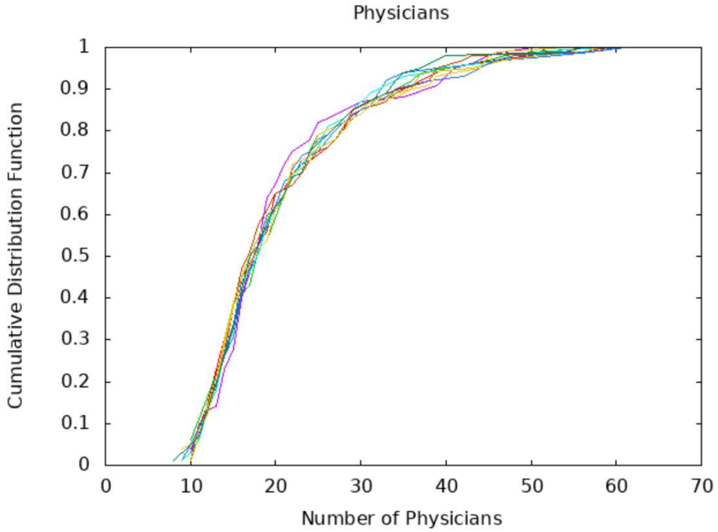
Determine how many samples are enough for the LHS

Work with decision maker to determine if the associated level of uncertainty in the statistics is acceptable

Analysis of Spread of Cumulative Distribution Functions

Compare range of the medians versus range of the 95th percentiles to determine if level of uncertainty in 95th percentiles is acceptable

Result: Confidence interval for the mean of the medians is tighter than the confidence interval on the mean of the 95th percentiles.



Example of replicate statistical analysis:

Range of 95th percentiles is [35, 43]
Mean of 95th percentile is 38.5
Confidence interval on the mean 95th percentile is [36.9,40.1]

Range of Medians is [17,18]
Mean of medians is 17.7
Confidence interval on mean of medians is [17.4,18]

Analysis of Number of Samples

Generate LHS samples of size N=100, N=500, and N=1000
Perform t-tests and F-tests to compare means and variances, respectively

Result: N=100 is sufficient to obtain reasonably accurate estimates of mean and variance

NumSamples	Statistic	FloorNurseMax	ICUNurseMax	PhysicianMax	RespiratoryTherap	BedMax	ICU_BedMax
100	Mean	27.30	52.02	21.00	17.00	171.71	69.40
	Std. Dev.	9.59	24.37	9.70	8.57	27.46	23.30
	Min	14	14	10	5	119	26
	Max	56	124	58	40	228	130
500	Mean	27.40	52.39	20.90	17.26	172.68	69.51
	Std. Dev.	9.66	25.30	9.89	9.93	28.01	23.37
	Min	13	15	8	3	108	29
	Max	61	137	70	58	254	137
1000	Mean	27.46	52.07	21.00	17.12	172.88	69.20
	Std. Dev.	9.71	24.89	10.15	9.71	28.05	23.21
	Min	12	14	8	3	112	25
	Max	62	130	69	64	249	134