Assessing sensitivity of intervention effects

MATHEMATICAL MODELING FOR INFECTIOUS DISEASE PLANNING IN AFRICA

60 minutes

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Questions: sensitivity analysis

Question 1: How sensitive are the intervention effects to changes in other parameter values?

Question 2. What parameters are most influential on the model outcomes?

Learning objectives

At the end of this lecture, you would:

1. Be able to assess the sensitivity of intervention effects to changes in one or more key parameters

2. Be able to interpret results on the sensitivity of intervention effects

Outline

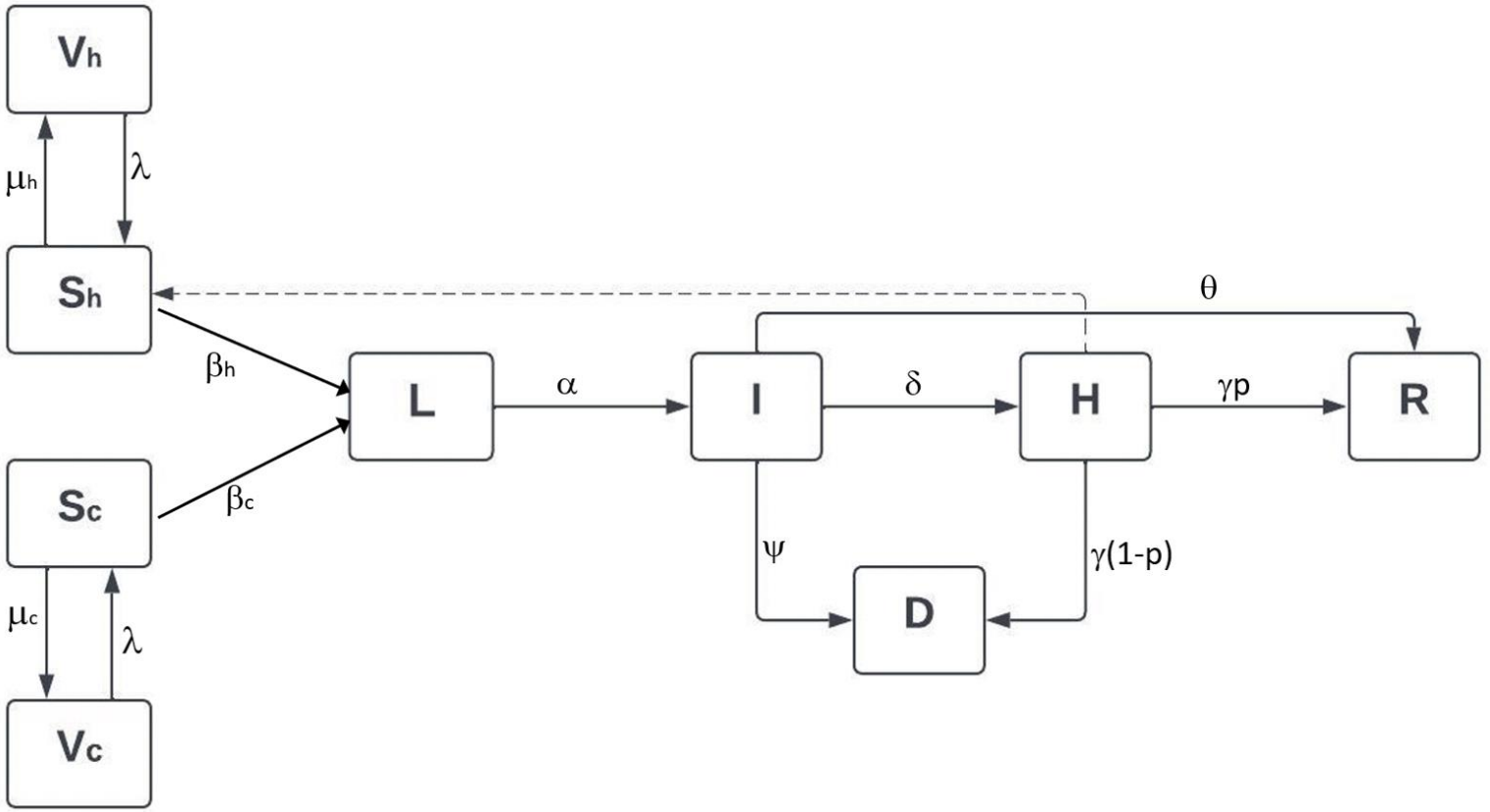
1. **Question 1**: How sensitive are the intervention effects to changes in other parameter values?

2. Demonstration with Berkeley Madonna

Slides on Question 2 are also provided (from slide 22) but will not be treated in this lecture.

Question 1: How sensitive are the intervention effects to changes in other parameter values?

Intervention: Surveillance



Compartmental diagram for an Ebola transmission model

Credit: Ebola Rwanda team

Relevant parameter: δ, rate at which infectious individuals are detected (and hospitalized)

Summary of surveillance effects

Total number of deaths by day 365	
$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
1244	82159

δ = hospitalization rate for infectious individuals (per day)

Conclusions based on results above: The higher surveillance rate (δ = 1/4) leads to reduced mortality, compared to the lower surveillance rate (δ = 1/8).

Assume we are uncertain about the transmission rate for frontliners, β_h.

What factors might influence this uncertainty?

- Uncertainty about per-contact infectivity
- Uncertainty about contact rates

How do we interpret our intervention effects (surveillance) considering this uncertainty?

What if we are uncertain about β_h?

- Will these conclusions hold if the transmission rate (β_h) is changed?
- Are the intervention effect results *sensitive* to changes in β_h?

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4	1244	82159

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Conclusion: Higher surveillance is better than lower surveillance for deaths.

How may we go about answering the above question?

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4	1244	82159
0		
0.25		
…		
3.25		
3.5		

Conclusion: Higher surveillance is better than lower surveillance for deaths.

Does the conclusion remain unchanged across different values of β_h?

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4	1244	82159
0	54	1879
0.25	72	2755
…	…	…
3.25	4637	184859
3.5	6908	213921

Conclusion: Higher surveillance is better than lower surveillance for deaths.

Does the conclusion remain unchanged across different values of β_h?

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Assessing the sensitivity of surveillance effects conclusions to changes in β_h

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0	54	1879
0.25	72	2755
…	…	…
3.25	4637	184859
3.5	6908	213921
	1436	**64886**

Baseline

Do we arrive at the same conclusions with the **summary** as we do with the **baseline**?

Summary (Column averages, excluding baseline)

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Conclusions

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4	1244	82159
0	54	1879
0.25	72	2755
…	…	…
3.25	4637	184859
3.5	6908	213921
	1436	**64886**

Surveillance effects are not sensitive to changes in β_h.

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

Main idea:

1. We will compare the interventions across different values of β_h and summarize the intervention results for each intervention.

2. The summary result (*Su*) will be compared to the baseline result (*Ba*).

3. If *Su* agrees with *Ba*, intervention effects are not sensitive to changes in β_h. However, if *Su* does not agree with *Ba,* intervention effects are sensitive to changes in β_h.

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

A note: The same procedure may be applied if interested in only a few values of β_h

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4	1244	82159
3.5	6908	213921

→ **Baseline**

Do we arrive at the same conclusions with **value 1** as we do with the **baseline**?

→ **Value 1**

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

For example,

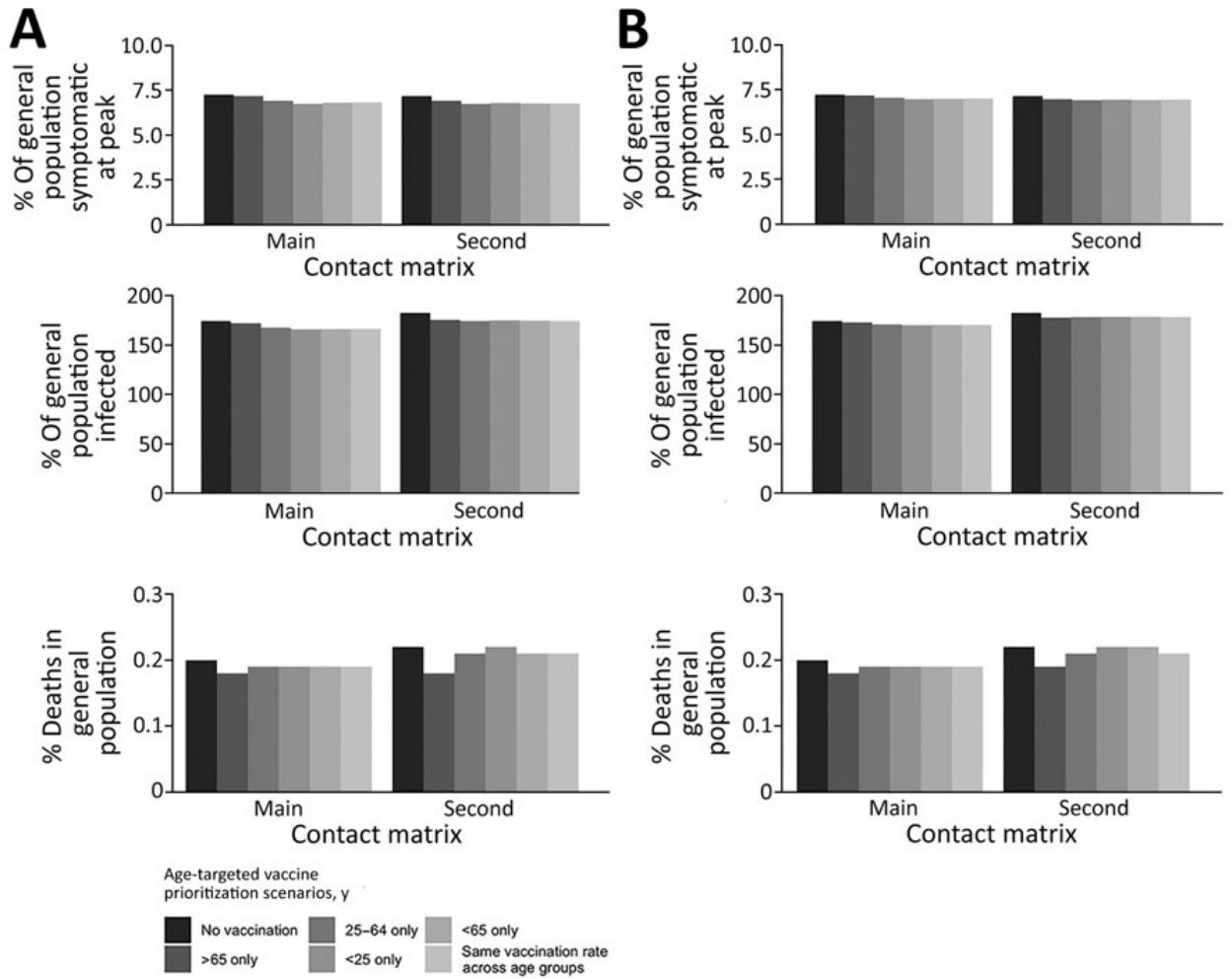


Figure 1. Effects of various vaccination scenarios on symptomatic infections at peak (upper panels), cumulative infections (middle panels), and deaths (lower panels) as a percentage of the general population, Ghana. The assessment used 2 different contact matrices in the main analysis and an effective reproductive number of 3.13 for the initial strain. A) Results assuming 1 million persons were vaccinated in 3 months. B) Results assuming 1 million persons were vaccinated in 6 months. Percentage of cumulative infections is >100% because of waning immunity from natural infection and vaccination.

Ofori SK, et al. Age-Stratified Model to Assess Health Outcomes of COVID-19 Vaccination Strategies, Ghana. Emerg Infect Dis. 2023;29(2):360-370. https://doi.org/10.3201/eid2902.221098

A procedure for assessing the sensitivity of intervention effects to changes in key parameters

Assessing the sensitivity of surveillance effects conclusions to changes in an uncertain parameter

Main idea:

1. We will compare the interventions across different values of the uncertain parameter (*p*) and summarize the intervention results for each intervention.

2. The summary result (*Su*) will be compared to the baseline result (*Ba*).

3. If *Su* agrees with *Ba*, intervention effects are not sensitive to changes in *p*. However, if *Su* does not agree with *Ba,* intervention effects are sensitive to changes in *p*.

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

Steps:

1. Write down your research question for this analysis: How sensitive are the results on surveillance effects to changes in β_h?

2. Decide on the model outcome for this analysis.

3. Write down the values of β_h to be assessed. (Refer to activity 1 where you defined bounds for key parameters)

4. Decide on the surveillance levels to be compared.

δ = hospitalization rate for infectious individuals (per day)
β_h = transmission rate for frontliners

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

Steps:

5. For each surveillance level, compute the model outcome for all values of β_h.

6. With the results from step 5, complete the table below.

Uncertain parameter

Values of interest for uncertain parameter

Model outcome

Intervention levels of interest

β_h	Total number of deaths by day 365	
	$\delta = 1/4$ day^{-1}	$\delta = 1/8$ day^{-1}
Baseline value: 2.4		
0		
0.25		
…		
3.25		
3.5		

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

Steps:

7. Summarize the results from step 6 separately for each surveillance level: compute an average of the model outcomes for each surveillance level.

8. Compare the summary results (*Su*) from step 7 to the baseline (*Ba*). If *Su* agrees with *Ba*, we may conclude that surveillance effects are not sensitive to changes in β_h. If *Su* does not agree with *Ba,* we may conclude that surveillance effects are sensitive to changes in β_h.

Assessing the sensitivity of surveillance effects conclusions to changes in β_h

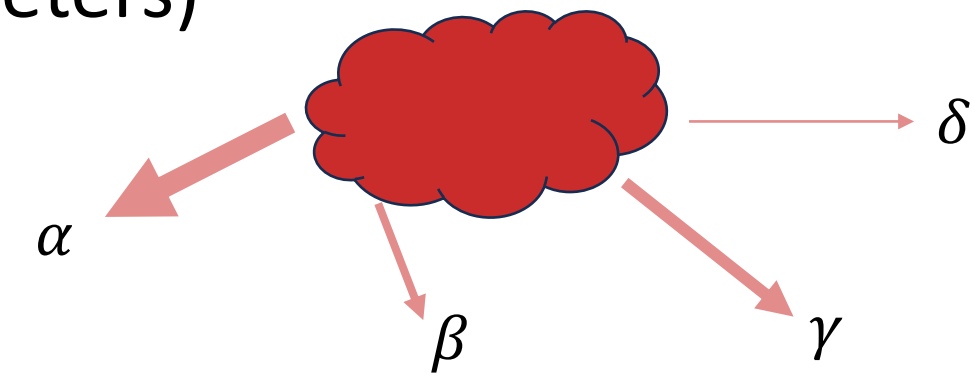
A demonstration in Berkeley Madonna using the outlined steps

Question 2. What parameters are most influential on the model outcomes?

A closer look at Question 2

- Could be interpreted as: *Where is the uncertainty in the model outcome coming from?*

- Analysis on question 2 quantifies how variation in the model outputs can be apportioned to the various inputs (or parameters)



Varying arrow widths are an illustration of differences in contributions of parameters to model uncertainty

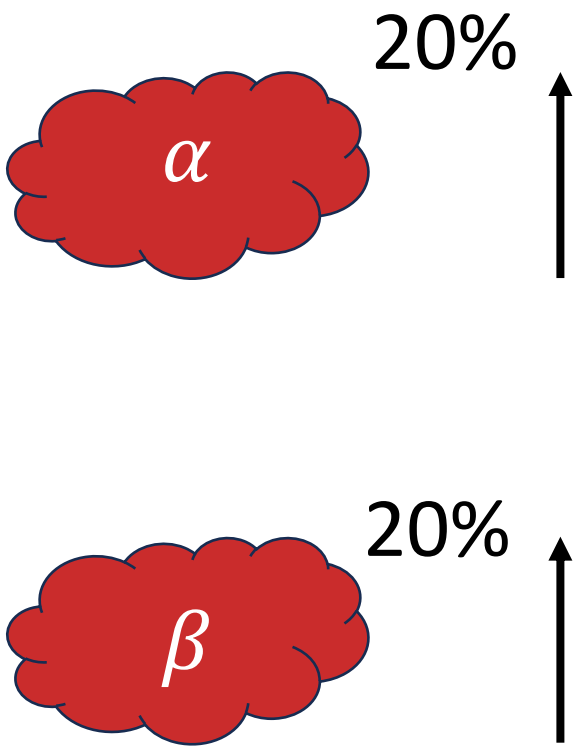
Reference: Saltelli and Annonni. (2010). Environmental Modelling & Software. https://doi.org/10.1016/j.envsoft.2010.04.012

Why sensitivity analyses?

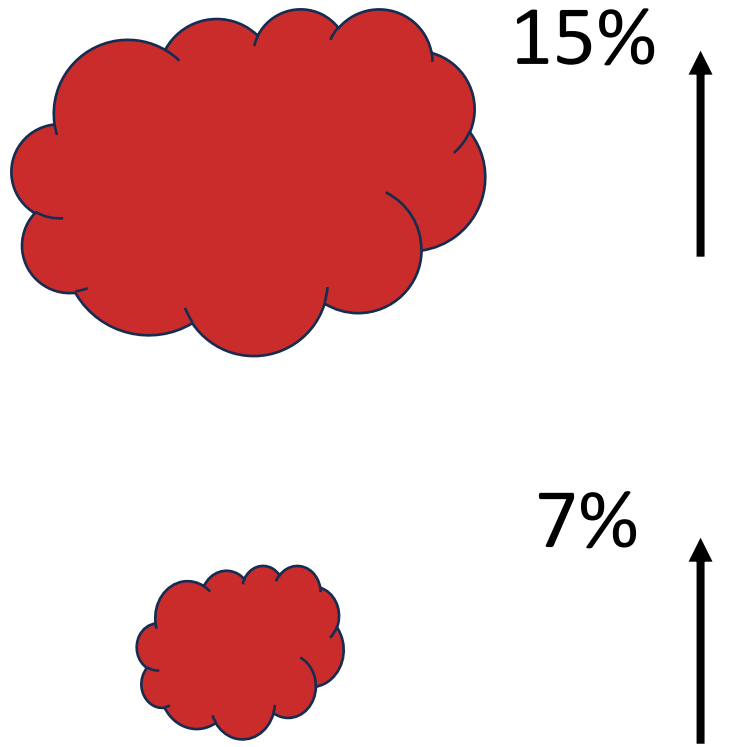
- To investigate how much variation in a parameter influences the variation in the model output
    - *How much of the uncertainty in model incidence is **explained** by the transmission rate parameter?*
    - Investigate parameter importance
    - If parameter is of biological/other significance, SA results allow us to make statements about the connection between the biological/other factors and the transmission process/outcomes of interest

Why sensitivity analyses?

Parameter uncertainty



Model output uncertainty



Sensitivity analyses vs uncertainty analyses

Sensitivity analyses (SA)	Uncertainty analyses (UA)
Question: Where is the uncertainty in the model inference coming from?	Question: How uncertain is the model inference (or estimate)?
Quantifies how variation in the model outputs can be apportioned to the various parameters	Characterizes the confidence bounds for a model output

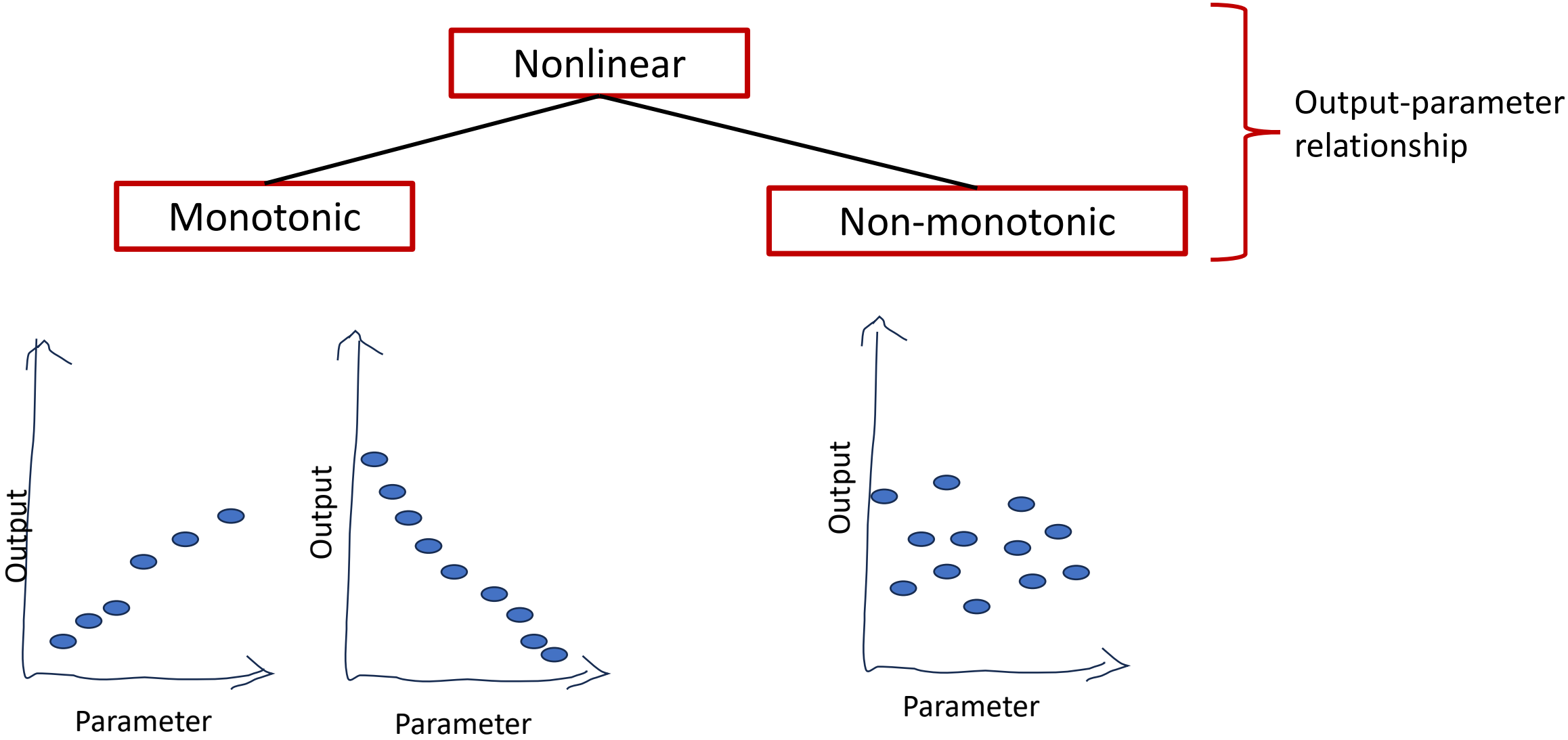
Reference: Saltelli and Annonni. (2010). Environmental Modelling & Software. https://doi.org/10.1016/j.envsoft.2010.04.012

In practice…

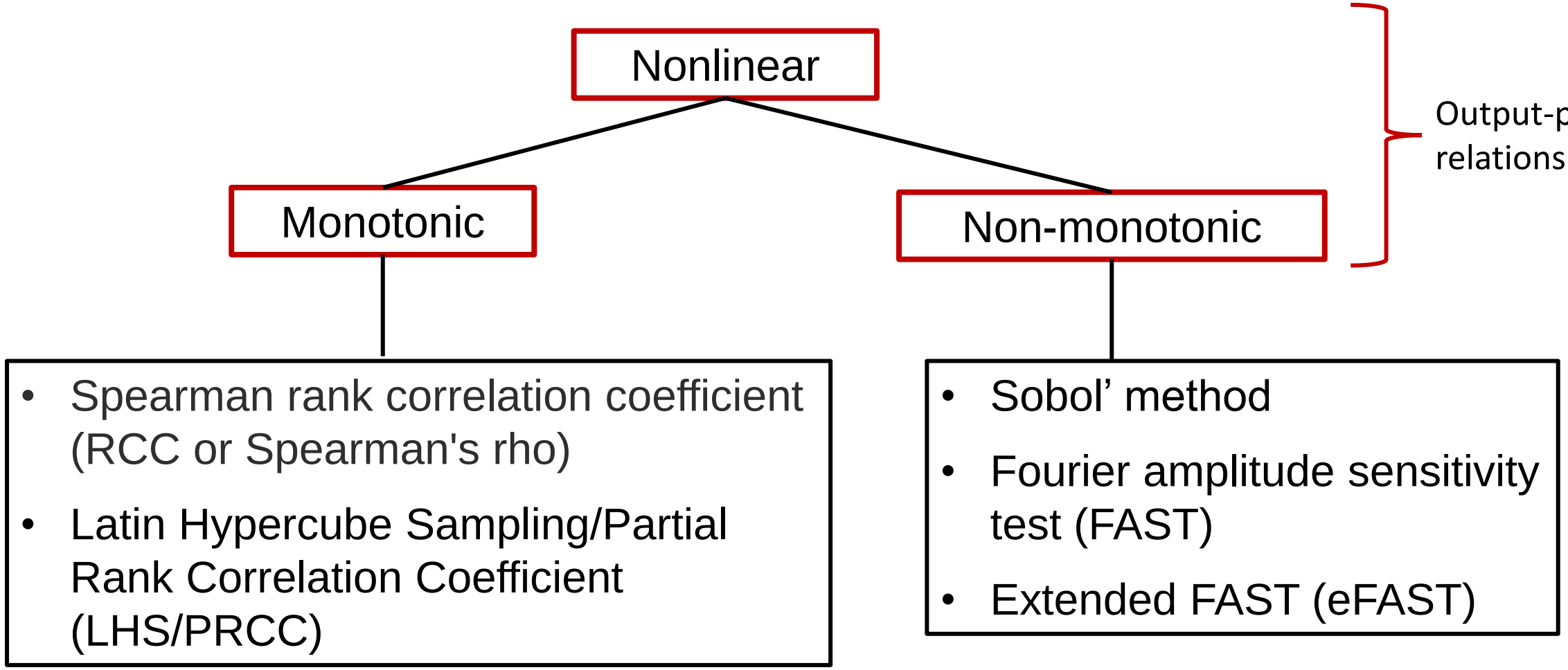
UA and SA are coupled and termed ”sensitivity analysis”, although they have different objectives.

Saltelli and Annonni. (2010). Environmental Modelling & Software.
https://doi.org/10.1016/j.envsoft.2010.04.012

Examples of SA methods



Examples of SA methods



Marino et al. (2008). Journal of Theoretical Biology.
https://doi.org/10.1016/j.jtbi.2008.04.011

One-at-a-time SA (OAT-SA) may not be reliable

- OAT-SA involves changing the value of a parameter OAT while keeping the others constant

- Why OAT-SA will not work with the models we are studying:

  - Assumes model is *linear* – in many cases, epidemic models are not
  - Does not consider interaction effects between parameters (simultaneous change of parameters is needed for interactions to be detected)
  - Does not sufficiently explore the parameter space (this problem is worse in higher dimensions)

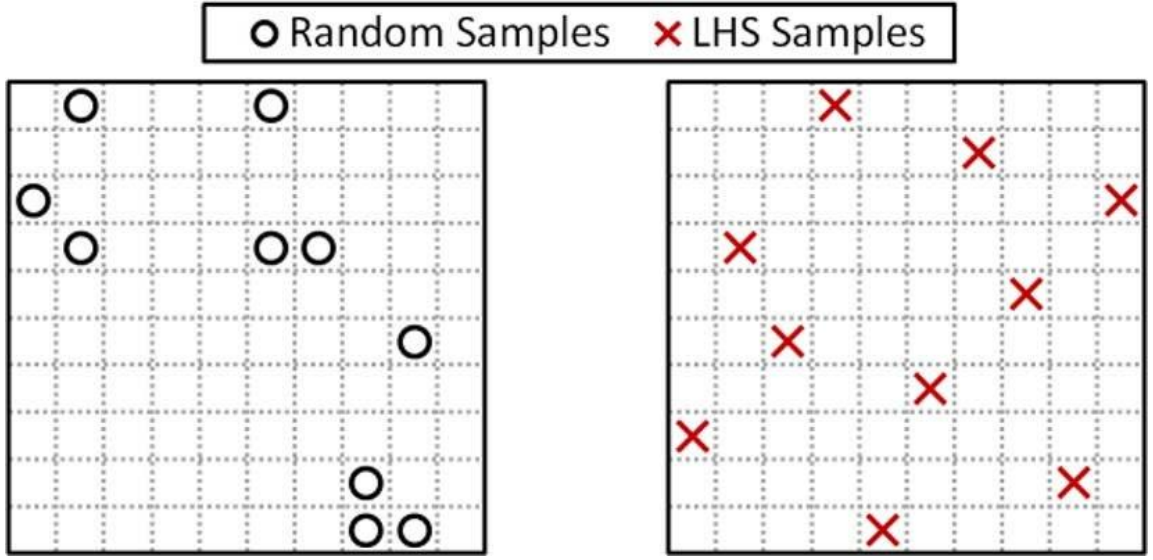
- See Saltelli and Annonni (2010) for proof

Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC)

General idea

- Efficiently explore parameter space (LHS)
- Identify and rank key parameters whose uncertainties contribute to model output uncertainty (PRCC)

LHS



- Sampling scheme

  1. Divide parameter range/space* into equally probable intervals
  2. Sample n times without replacement from each interval

- Explores the parameter space more efficiently than simple random sampling

*The figure assumes a two-dimensional parameter space.

LHS: McKay et al. (1979). *Technometrics*. https://doi.org/10.2307/1268522
Figure reference: Preece and Milanović (2015). *IEEE Transactions on Power Systems*. https://doi.org/10.1109/TPWRS.2015.2417204

Partial Rank Correlation Coefficient

- Correlation
  - Strength of linear association between parameter and output

- Partial correlation
  - Correlation between a parameter and an output while discounting the linear effects of other parameters on the output

- Partial rank correlation
  - Partial correlation computed on *rank-transformed data (why transform?)*

Condition: Little to no correlation between parameters

LHS meets PRCC

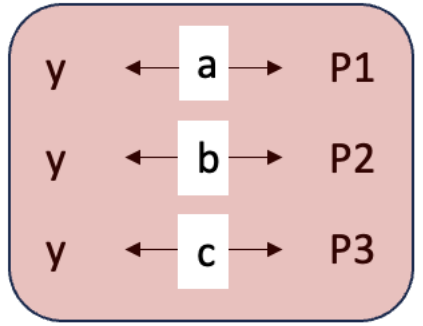
1. Set ranges for each parameter and get LHS samples.

Parameter		
P1	**P2**	**P3**
0.5	0.7	0.02
…	…	0.05
…	…	…

2. Compute model output (y) for each LHS sample and rank transform all results.

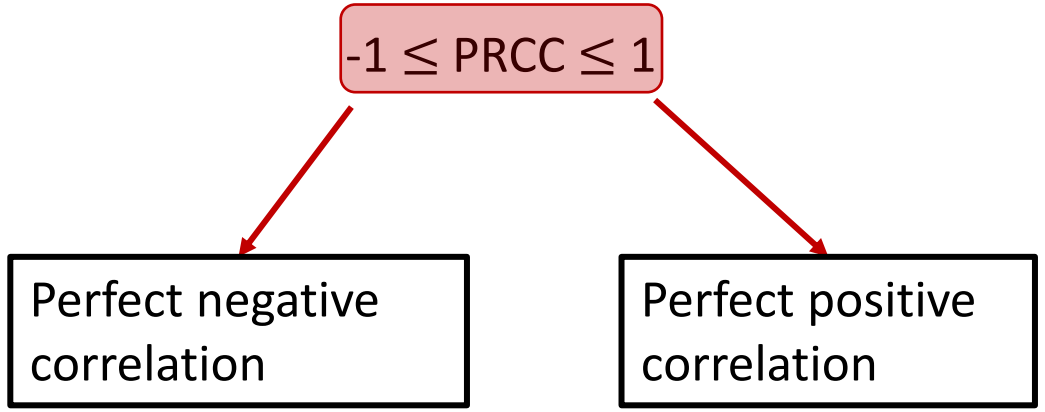
P1	**P2**	**P3**	**y**
0.5	0.7	0.02	1
…	…	0.05	3
…	…	…	…

3. Compute the partial correlation between output and each parameter.



$-1 \leq a, b, c \leq 1$

4. Interpret, considering statistical significance:



Activity: Discuss an application of LHS/PRCC to a cholera model

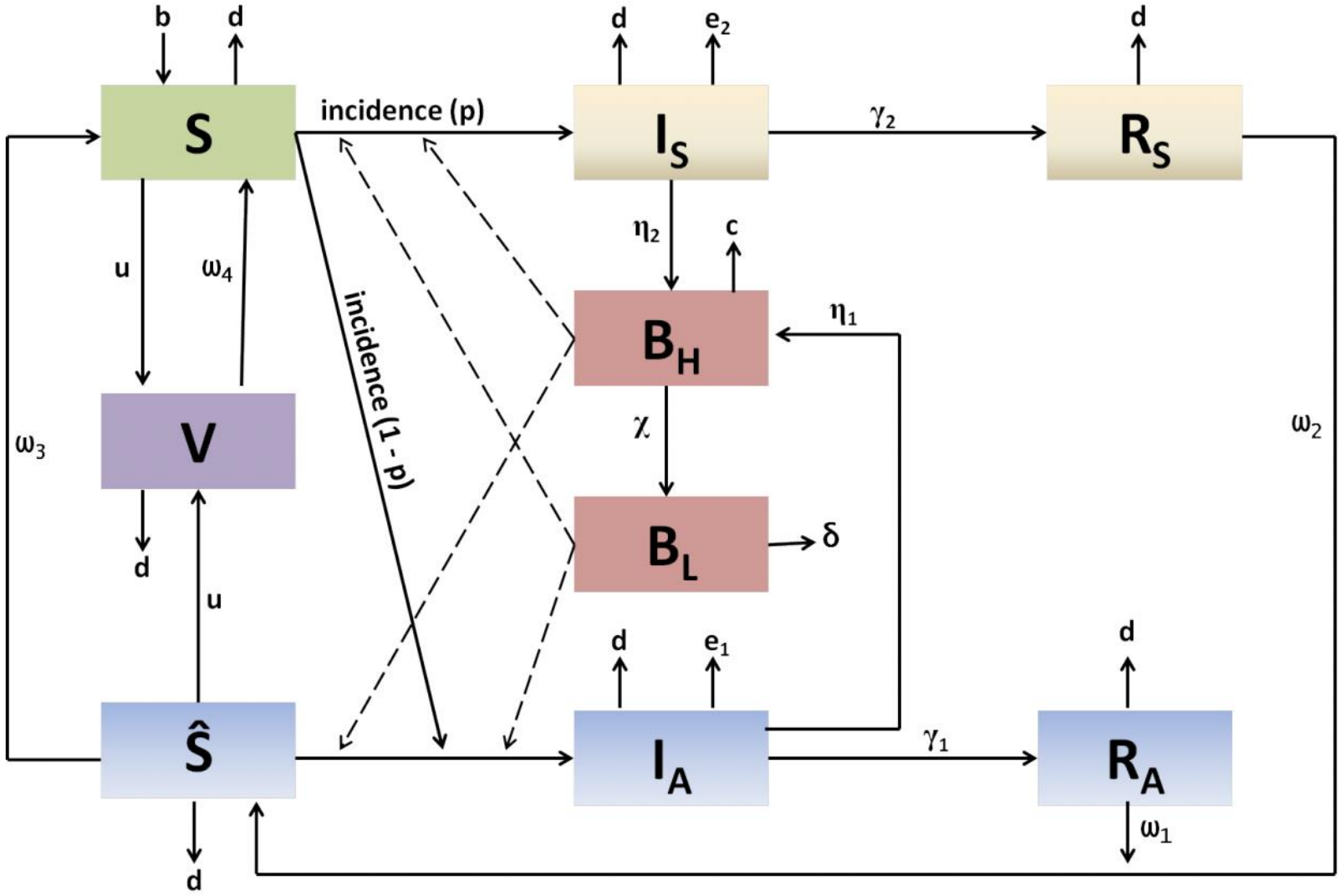
Application of LHS/PRCC to a cholera model

Outline

1. Model structure
2. Outcomes of interest
3. Testing monotonicity assumptions
4. LHS parameter ranges
5. LHS/PRCC results

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

Cholera transmission model



Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

Parameter table

Table 3.1: Parameter List for Cholera Epidemic Model.

Symbol	Description	Value
$\hat{S}_0$	Initial # susceptible humans with partial immunity	3000
S_0	Initial # susceptible humans without partial immunity	$10,000 - \hat{S}_0$
I_{A0}	Initial # asymptomatic infecteds	0
I_{S0}	Initial # symptomatic infecteds	0
R_{A0}	Initial # recovered humans (asymptomatic)	0
R_{S0}	Initial # recovered humans (symptomatic)	0
V_0	Initial # humans with vaccinated immunity	0
B_{H0}	Initial concentration of highly infectious (HI) vibrios in environment	0
B_{L0}	Initial concentration of non-highly infectious (non-HI) vibrios in environment	$\kappa_L/2$
p	Probability of infecteds moving from symptomatic class to infected class without partial immunity	0.6
r	Scaling factor used to compute β_H from β_L.	0.1
β_L	Ingestion rate of non-HI vibrio from environment	0.008 day^{-1}
β_H	Ingestion rate of HI vibrio from environment.	$r * \beta_L$ day^{-1}
κ_L	Half saturation constant of non-HI vibrios	103 cells/ml
κ_H	Half saturation constant of HI vibrios	$\kappa_L/700$ cells/ml

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

Parameter table continued

e_1	Cholera-related death rate for asymptomatic infecteds	$e_2/20$ day^{-1}
e_2	Cholera-related death rate for symptomatic infected	0.03 day$^{-}1$
γ_1	Cholera recovery rate (asymptomatic)	0.75 day^{-1}
γ_2	Cholera recovery rate (symptomatic)	0.1 day^{-1}
ω_1	Rate of waning cholera immunity from asymptomatic infecteds to susceptibles with partial immunity	$1/180$ day^{-1}
ω_2	Rate of waning cholera immunity from symptomatic infecteds to susceptible humans with partial immunity	$1/(365 * 2)$ day^{-1}
ω_3	Immunity waning rate: susceptibles without partial immunity $\rightarrow$ susceptibles with partial immunity	$1/(10 * 365)$ day^{-1}
ω_4	Immunity waning rate: humans with vaccinated immunity $\rightarrow$ susceptibles without partial immunity	0.001 day^{-1}
s	Scaling factor used to compute η_2 from η_1	100
η_1	Rate of contribution to HI vibrios in environment by asymptomatic infecteds	0.008 cells/ml-day-human
η_2	Rate of contribution to HI vibrios in environment by symptomatic Infected.	$s * \eta_1$ cells/ml-day-human
χ	Transaction rate of vibrios from HI to non-HI state	5 day^{-1}
d	Death rate of vibrios	$1/30$ day^{-1}
u	Rate at which susceptible and asymptomatic infecteds are vaccinated daily	0 day^{-1}
b	Natural birth rate of humans	$0.03/365$ day^{-1}
d	Natural death rate of humans	$0.02/365$ day^{-1}

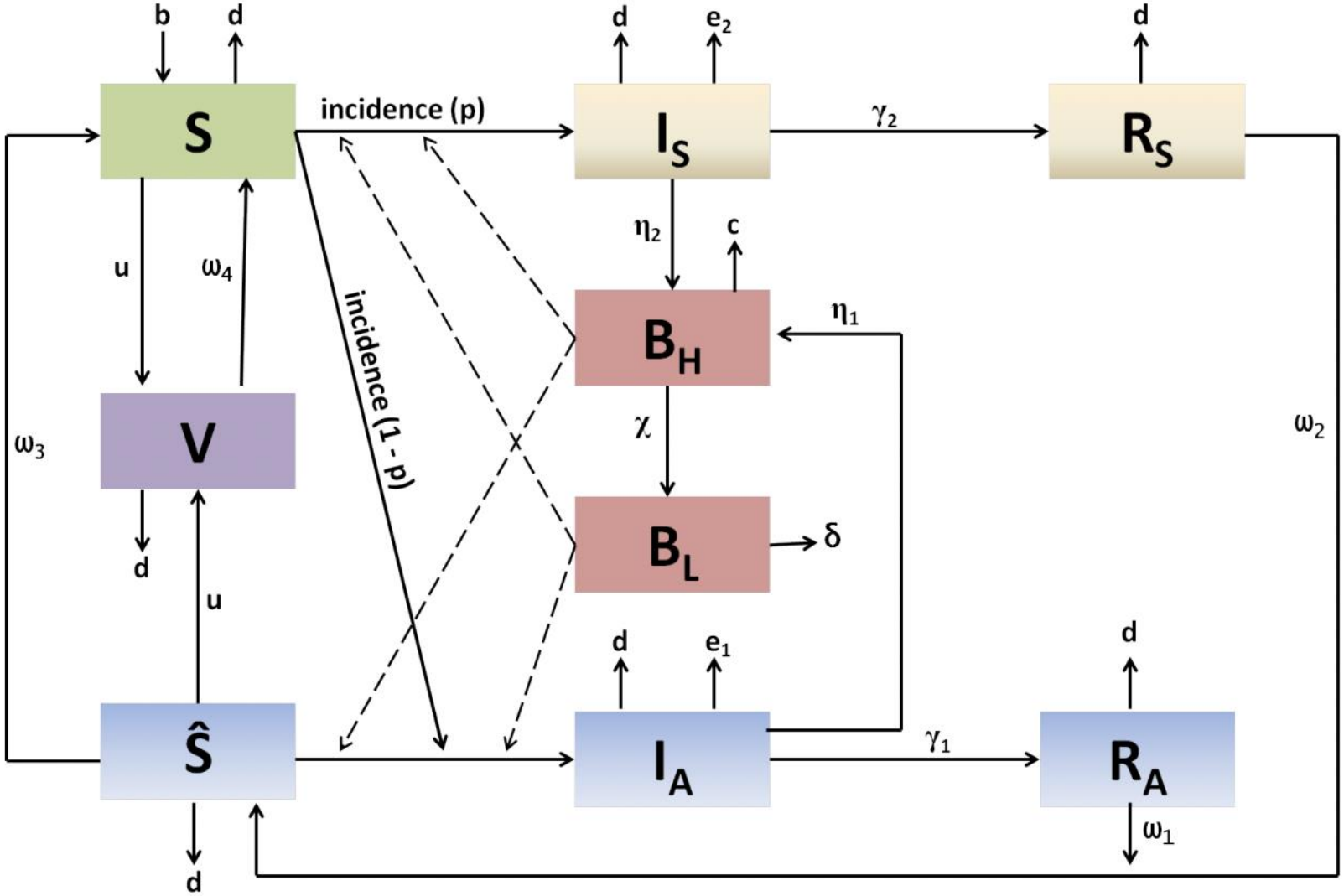
Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

Outcomes of interest

1. Total number of infected individuals
2. Total number of symptomatic infected individuals

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

Make a guess: which parameters will be most influential on the outcomes of interest, and by how much?



Outcomes of interest:

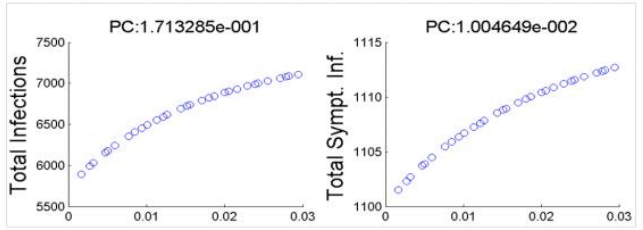
1. Total number of infected individuals
2. Total number of symptomatic infected individuals

Comments on question above

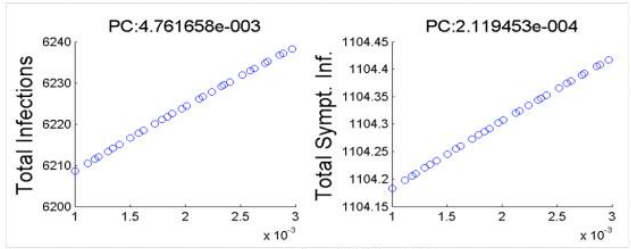
- Difficult to tell by observation!
- PRCC allows us to get answers using a principled procedure.

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

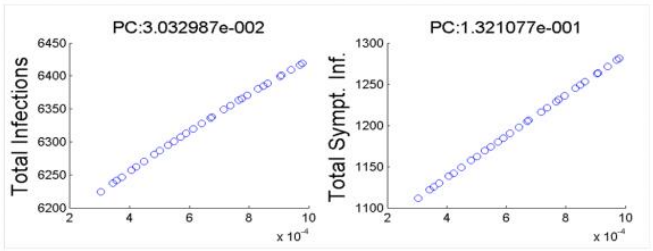
Testing monotonicity assumptions



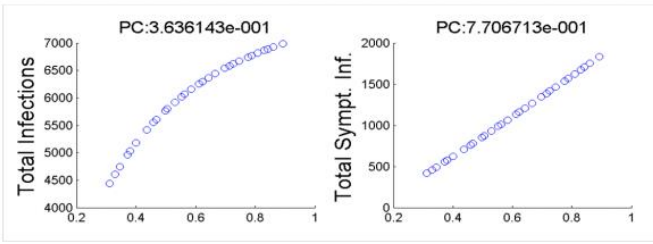
ω_1: waning RA to SH



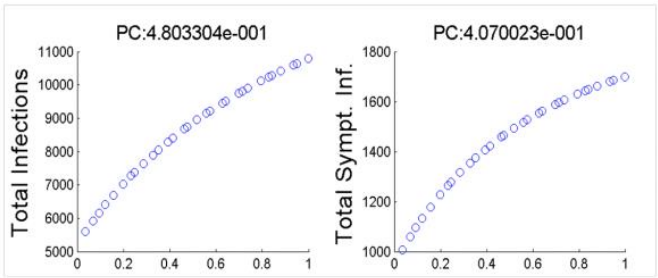
ω_2: waning RS to SH



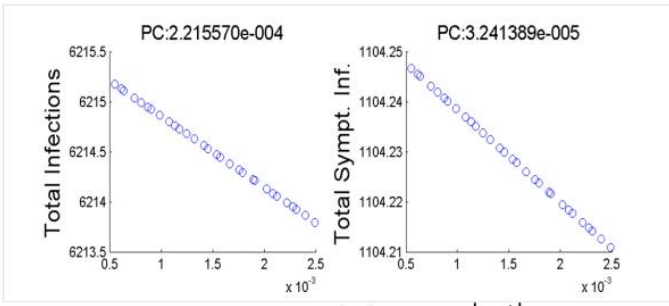
ω_3: waning SH to S



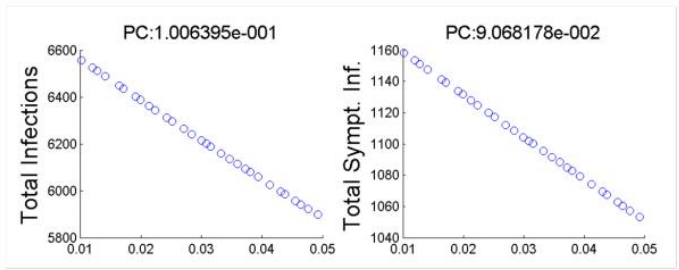
p: prop sym



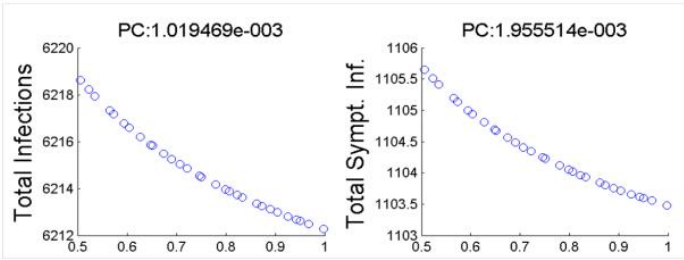
$\beta_H = r^*\beta_L$



e_1: asymp death



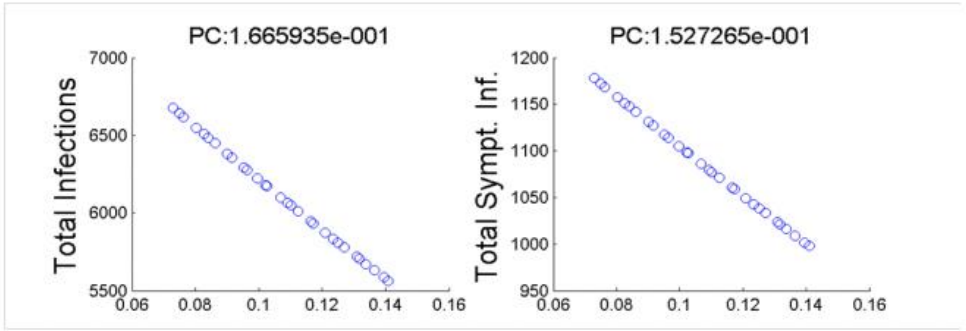
e_2: symp death



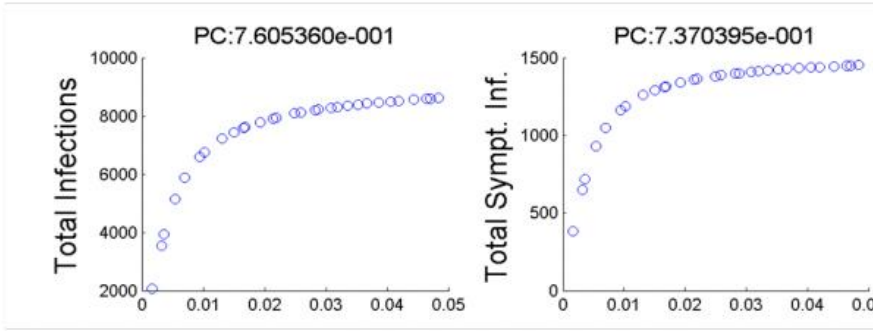
γ_1: asymp recovery

Figure 3.2: Monotonicity plots for ω_1, ω_2, ω_3, p, β_H, e_1, e_2, and γ_1

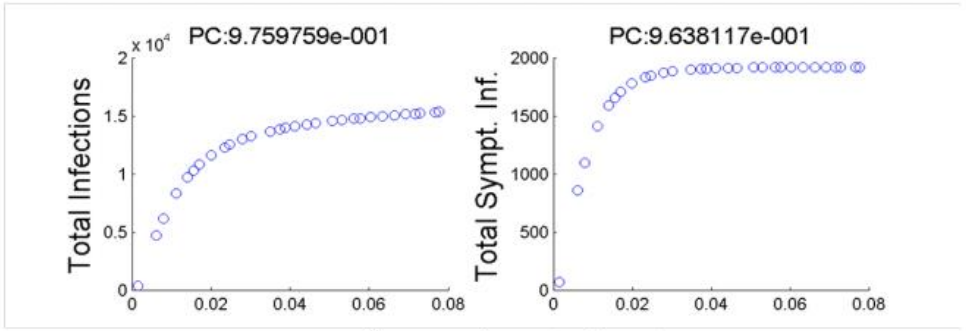
Testing monotonicity assumptions (continued)



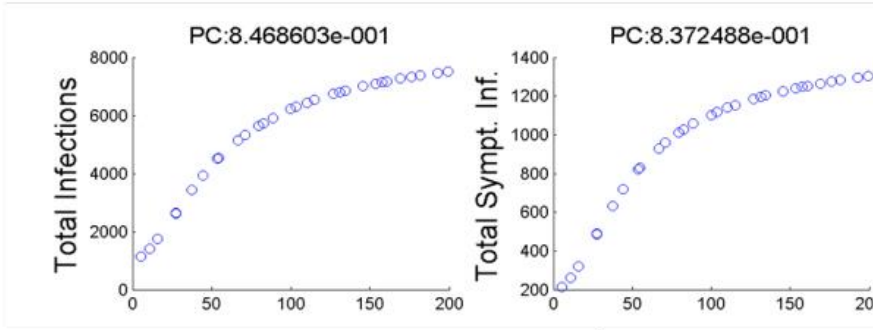
γ_2: symp recovery



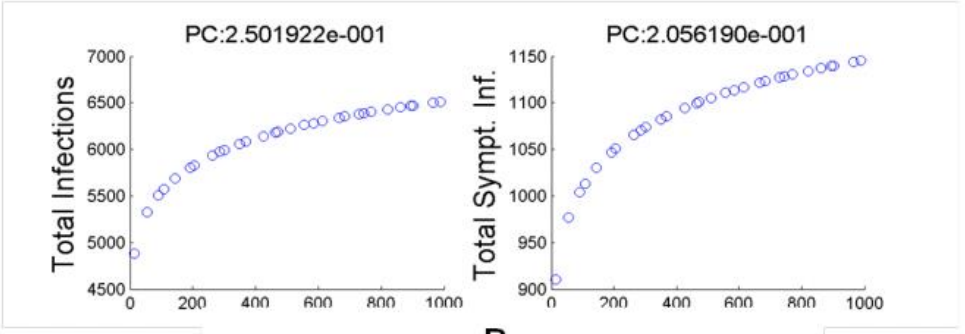
η_1



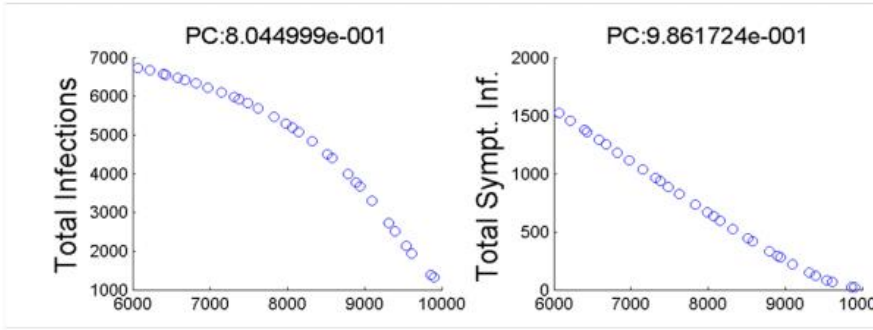
β_L = low infectious



$\eta_2 = s^*\eta_1$



B_{L0}



S_0

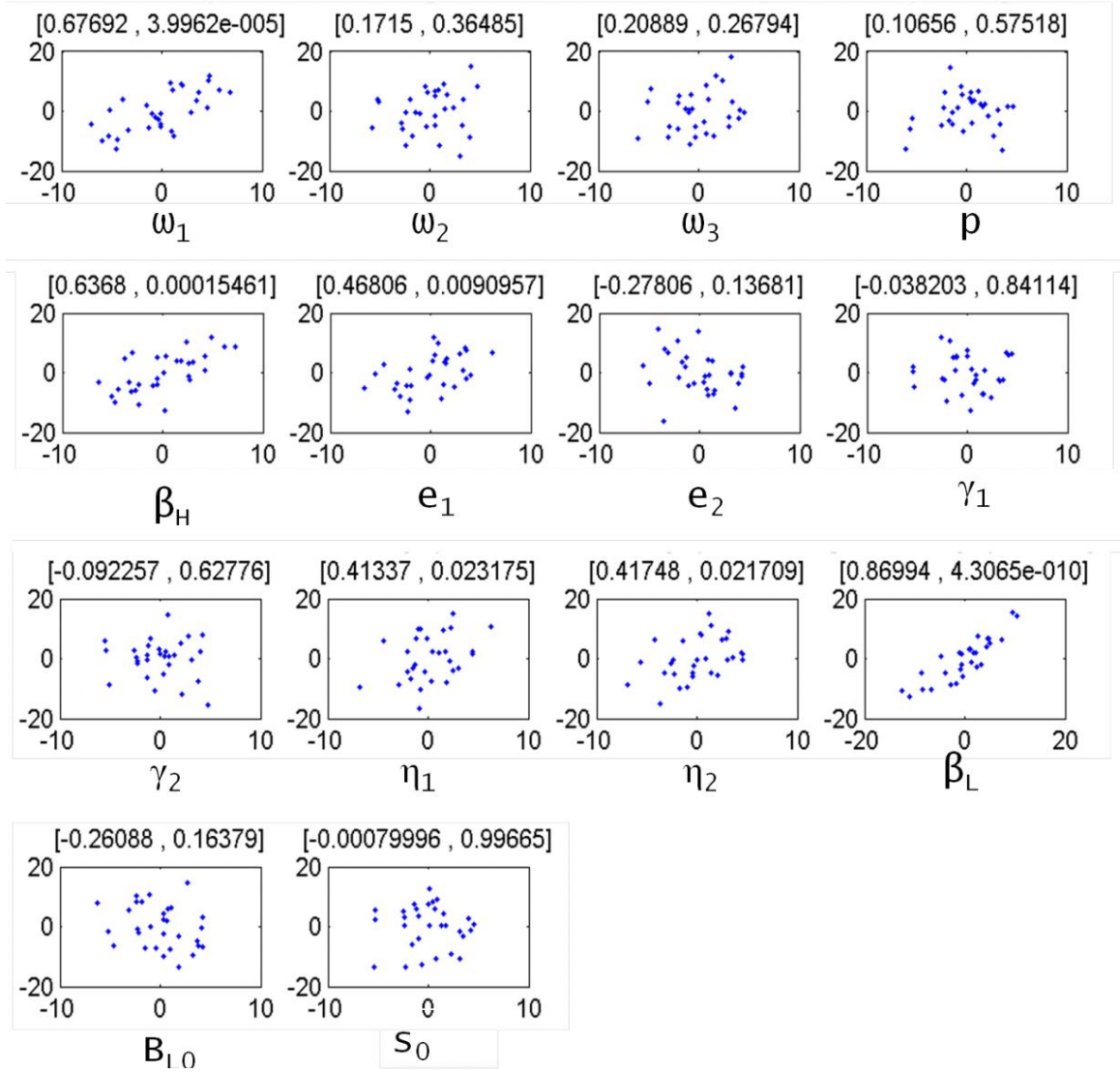
Figure 3.3: Monotonicity plots for γ_2, η_1, η_1, β_L, η_2, B_{L0}, and S_0

LHS parameter ranges

Parameter	Min	Baseline	Max
ω_1	0.001	$1/180$	0.03
ω_2	0.001	$1/(2*365)$	0.003
ω_3	0.0003	$1/(10*365)$	0.001
p	0.3	0.6	0.9
r	0.01	0.1	1
e_2	0.01	0.03	0.05
$e_1 = e_2/20$	0.0005	0.0015	0.0025
γ_1	$1/2$	0.75	1
γ_2	$1/14$	0.1	$1/7$
η_1	0.0001	0.008	0.05
η_2	1	100	200
s	0.001	0.008	0.08
B_{L0}	$\kappa_L/500$	$\kappa_L/2$	κ_L
S_0	6000	10000 - $\hat{S}_0$	10000

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

LHS/PRCC results

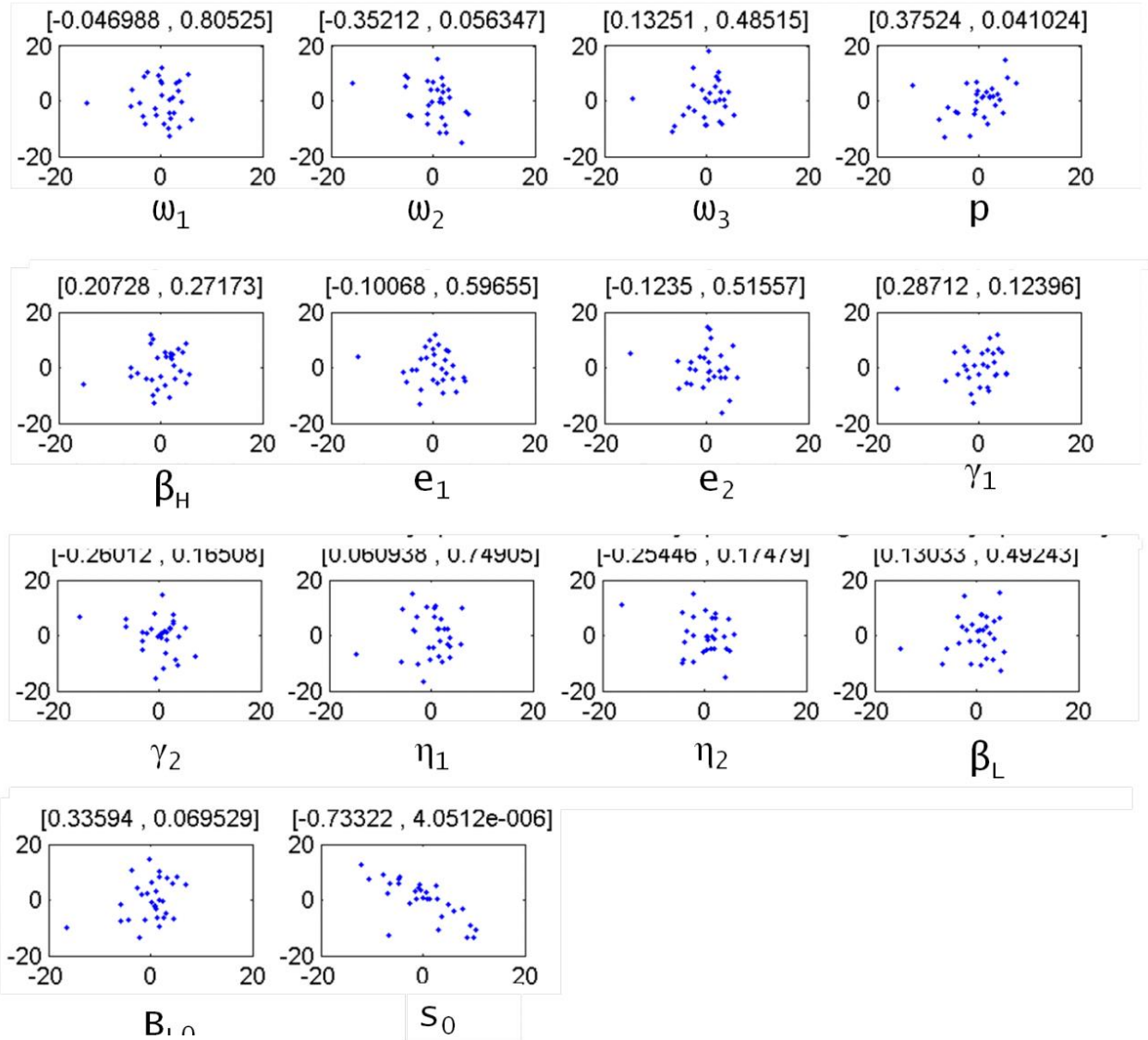


PRCC Plots for Total Infecteds.

Annotations on top of plots: [PRCC, p-value]

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

LHS/PRCC results



PRCC Plots for Total Symptomatic Infecteds.

Annotations on top of plots: [PRCC, p-value]

Gomero, Boloye, "Latin Hypercube Sampling and Partial Rank Correlation Coefficient Analysis Applied to an Optimal Control Problem. " Master's Thesis, University of Tennessee, 2012.

LHS/PRCC results

Parameters	Total Infectious		Total Symptomatic Infecteds	
	PRCC	*p-value*	*PRCC*	*p-value*
ω_1: Waning R_A to $\hat{S}$	*0.67692	4.00E-05	-0.04699	0.80525
ω_2: Waning R_S to $\hat{S}$	0.1715	0.36485	-0.35212	0.056347
ω_3: Waning $\hat{S}$ to S	0.20889	0.26794	0.13251	0.48515
p: Prop. Sympt.	0.10656	0.57518	0.37524	0.041024
$\beta_H = r * \beta_L$	*0.6368	0.000155	0.20728	0.27173
e_1:Asympt. death rate	0.46806	0.009096	-0.10068	0.59655
e_2:Sympt. death rate	-0.27806	0.13681	-0.1235	0.51557
γ_1	-0.0382	0.84114	0.28712	0.12396
γ_2	-0.09226	0.62776	-0.26012	0.16508
η_1	0.41337	0.023175	0.060938	0.74905
$\eta_2 = s * \eta_1$	0.41748	0.021709	-0.25446	0.17479
β_L: Low infectious	***0.86994	4.31E-10	0.13033	0.49243
B_{L0}	-0.26088	0.16379	0.33594	0.069529
S_0	-0.0008	0.99665	**-0.73322	4.05E-06

(*) is used to indicate possible contributors (PRCC values: ~0.5 to 0.69 or -0.5 to -0.69), (**) is used to indicate very likely contributors to uncertainty (PRCC values: ~0.7 to 0.79 or -0.7 to -0.79) and (***) is used to indicate highly likely contributors to uncertainty (PRCC values: ~0.8 to 0.99 or -0.8 to -0.99). Grey shaded boxes are s

Alternative means of presenting PRCC results

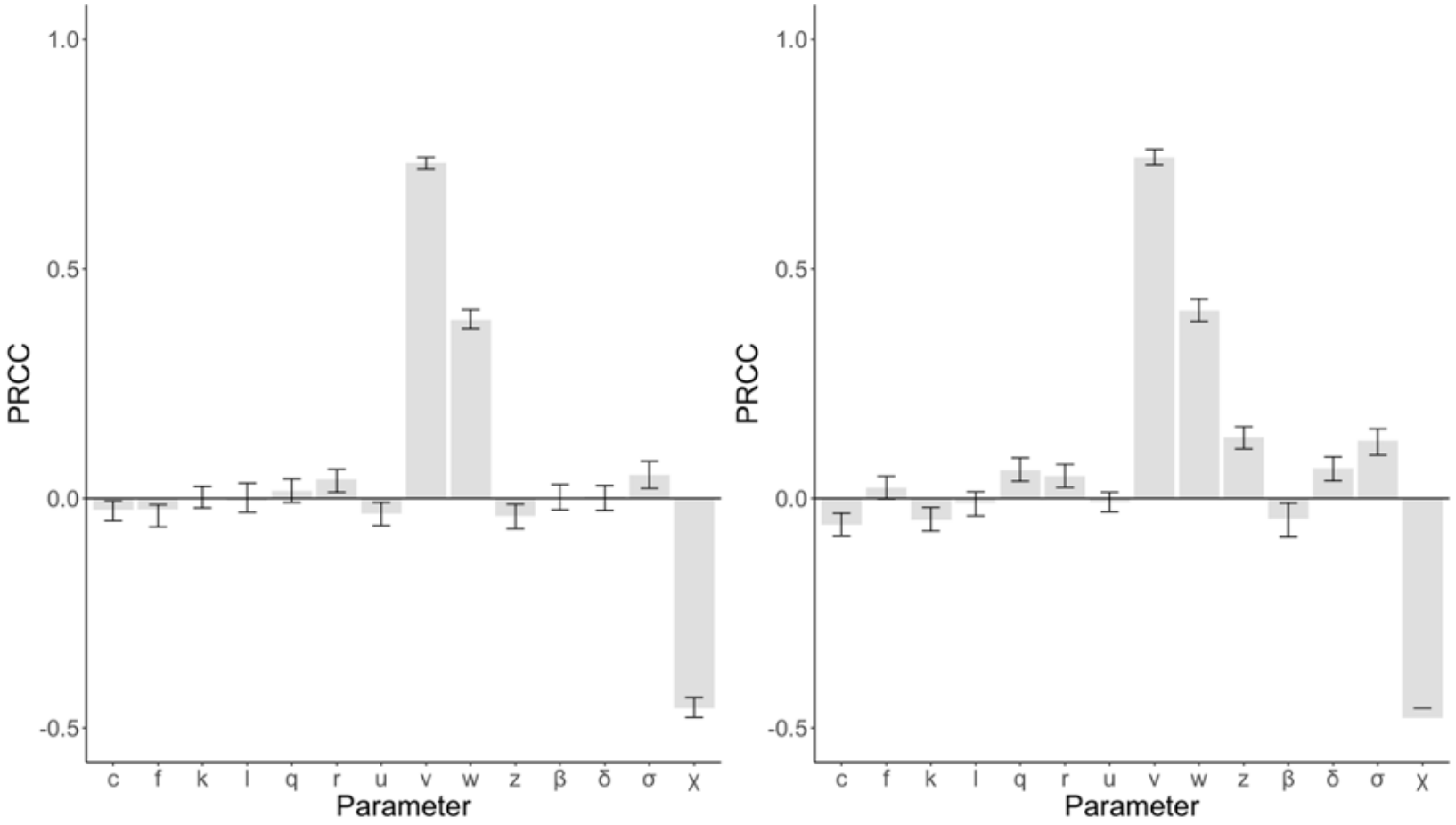


Figure: Global sensitivity analysis of the impact of parameters on cumulative infections (left panel) and deaths averted (right panel) over the range of daily vaccination rate using Partial rank correlation coefficient (PRCC).

Ofori et al. Modeling the Health Impact of Increasing Vaccine Coverage and Nonpharmaceutical Interventions against Coronavirus Disease 2019 In Ghana. *In press.*