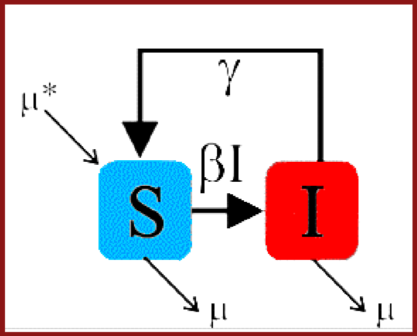
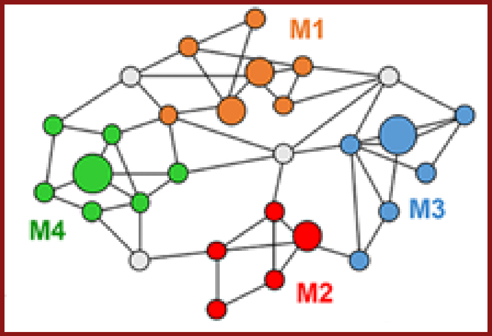
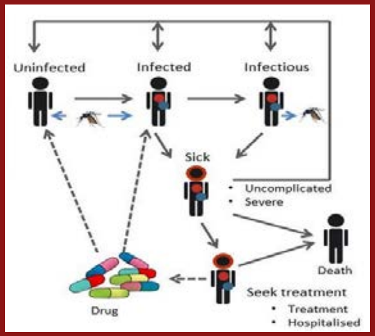
Stochastic Elements in Models to Support Disease Control Policy

How Much Detail is Enough?







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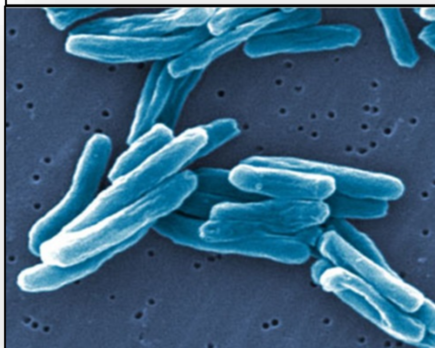
Agenda

- Motivation
- Case study: HIV vaccine
  - Methods
  - Results
  - Discussion
- Final thoughts

Communicable diseases: 20% of deaths

TB



1.7 million

Malaria

430,000

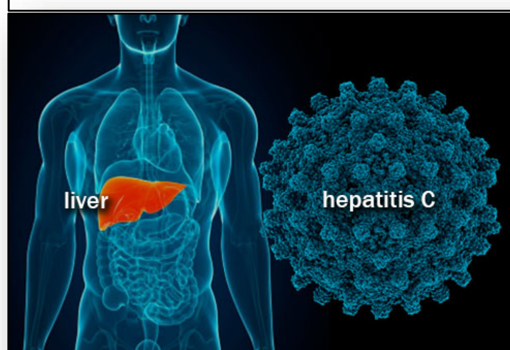
HIV

1.0 million

Cholera

140,000

Hepatitis C



400,000

Measles

100,000

Spread of communicable diseases

- Different transmission modes
  - Person-to-person or vector-borne
  - Bloodborne, airborne, foodborne, …
  - Sexual contact, needlesharing, perinatal, casual contact, food or water, mosquitoes, …
- Stochastic spread
  - Depends on contacts and probability of transmission per contact
- Nonlinear dynamics
  - E.g., number infected over time may be an S-shaped curve

Communicable disease spread is a stochastic, dynamic, nonlinear process

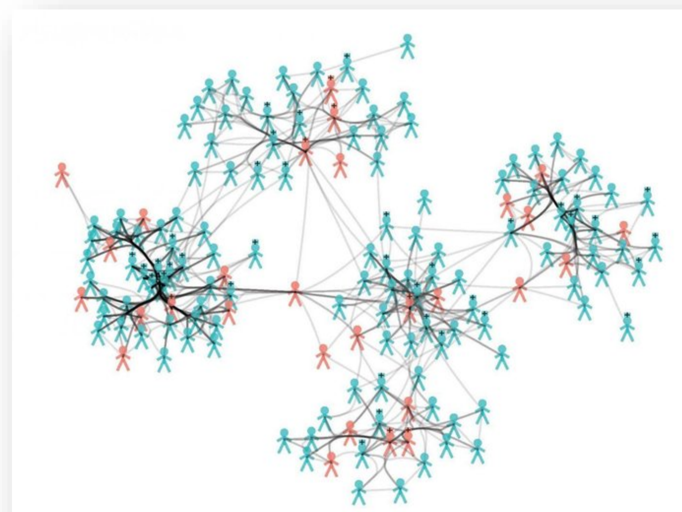
Control of communicable diseases

- Prevention (behavior change, sanitation, vaccines, vector control …)
- Treatment (cure or suppress)
- Models can evaluate the impact of alternative control policies
- Resources are always limited
- Models can help determine the appropriate allocation of disease control resources

Unanswered questions

How can we best model the spread of communicable diseases in order to inform good policy decisions?

What level of model detail – stochastic or otherwise – is appropriate?



Example: HIV

- 37 million people living with HIV, 1.8 million new infections per year
- Bloodborne: Spread from mother to child, via sexual contact, needlesharing contact, transfusion
- Many localized epidemics

HIV policy questions

- 1.8 million new infections per year
  - What programs should we invest in to prevent the spread of HIV?
- 45% of infected individuals do not receive treatment
  - How should we allocate scarce treatment funds?
- For every person entering treatment, two new infections occur
  - What is the appropriate allocation of resources between prevention and treatment?

Models to support HIV policy

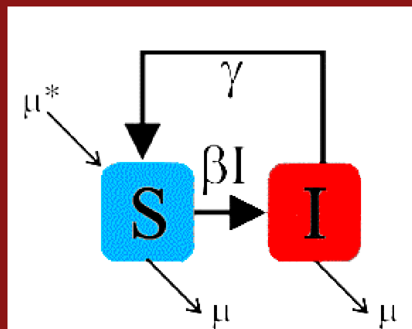
- Epidemic/disease models are frequently used to assess potential HIV prevention and treatment policies
  - Many types of models (Markov, compartmental, network, microsimulation, agent-based, …)
- Models instantiated with best available data
- Sensitivity analysis performed on uncertain variables (one-way, multi-way, stochastic, …)

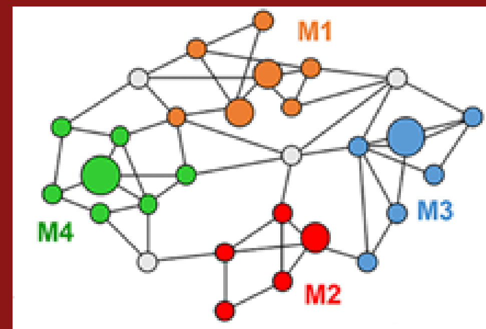
Example policy conclusions

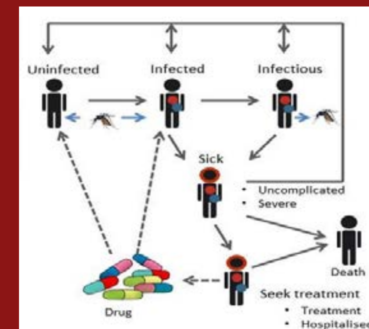
- HIV pre-exposure prophylaxis for people who inject drugs (PWID) is effective but not cost-effective (deterministic compartmental model)
- HIV pre-exposure prophylaxis for high-risk PWID can be cost-effective (stochastic network model)
- Where malaria is prevalent, daily cotrimoxazole for all HIV-infected pregnant women is cost-effective (individual microsimulation)
- We will be able to eradicate HIV by getting enough people on treatment (various model types)

To what extent do these conclusions depend on the model that was used?

Structural uncertainty







Consensus in the literature that "… model and methodological assumptions can have greater impact on results than parameter estimates, although sensitivity analyses are rarely performed on these sources of uncertainty."

How much complexity is needed?

- A model should be only as complex as is necessary
  … what is necessary?
- A model should be simple but “not so simple that realistic violation of simplifying assumptions will change an inference”

Addressing structural uncertainty

- Frameworks for addressing/presenting model structure
  - Bilke et al (2011) propose a standard framework for addressing and presenting uncertainty in decision models
  - Jackson et al (2011) suggest using a comprehensive model that includes all parameters; then scale back
- Modeling consortia compare outcomes of different models
  - Cancer Intervention and Surveillance Modeling Network (CISNET), HIV Modelling Consortium, …
  - Collect and compare predictions across models that vary in scope, parameters, structure

Addressing structural uncertainty

- Examine effects of different choices in epidemic models
  - Rahmandad et al (2008) compare a dynamic compartmental model to agent-based models with different network structures
  - White et al (2009) compare a simple deterministic model to more complex models used to evaluate malaria elimination strategies
  - Silal et al (2016) compare impact of interventions in different SEIS models (e.g. for malaria control)
  - Suen et al (2017) compare effects of risk stratification in SI compartmental models, and intervention impact

Addressing structural uncertainty

- Inference robustness assessment (Koopman 2004)
  - Systematic approach for isolating the effects of structural choices in a model
  - Contact/simulation complexity and parameter complexity
  - Relax an assumption gradually over a family of linked models
  - Examine how inferences from the models change

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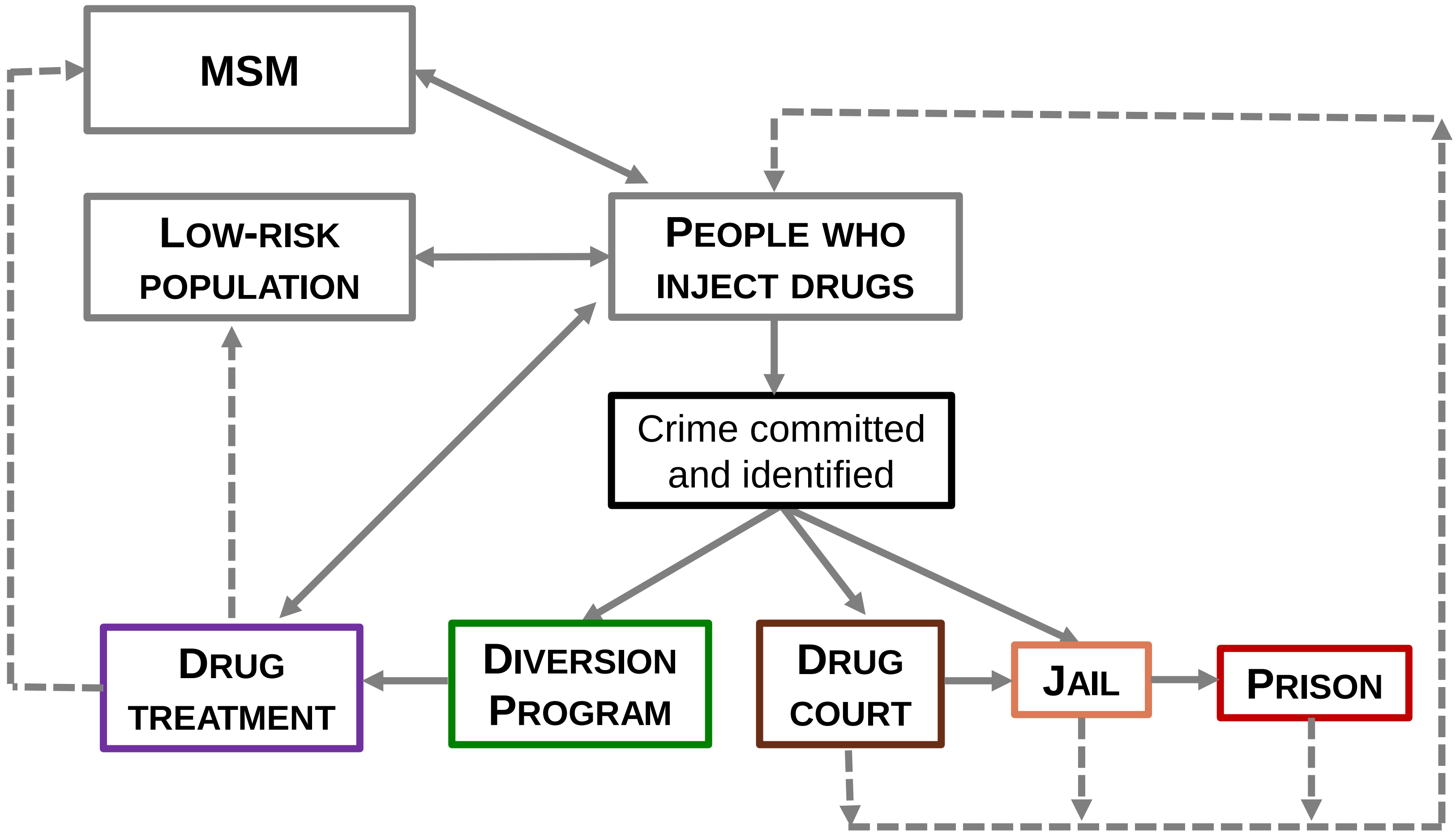
Overview

- What would be the effectiveness and cost-effectiveness of a potential HIV vaccine in Seattle?
- Case study using inference robustness assessment
- 8 linked models of HIV
  - Differ by contact/simulation complexity, parameter complexity
  - Calibrated to achieve similar projections

HIV in Seattle

- Key risk groups: MSM, PWID
- HIV prevalence
  - 0.01% in general population
  - 17% among MSM
  - 8% among PWID
- Hepatitis C (HCV) is co-epidemic
  - 8% among MSM
  - 63% among PWID
- LEAD program: Low-level drug offenders diverted into community-based care

Population subgroups and disease risks



How to model the spread of HIV to support policy decisions?

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Methods

- 8 linked HIV models instantiated for King County, Washington
- Core risk groups: Low risk, MSM, PWID, PWID/MSM
- HIV transmission: sexual, needlesharing
- Contact/simulation complexity
  - Deterministic compartmental model → stochastic network microsimulation
- Parameter complexity
  - HIV → age, HCV → PWUD, race, incarceration

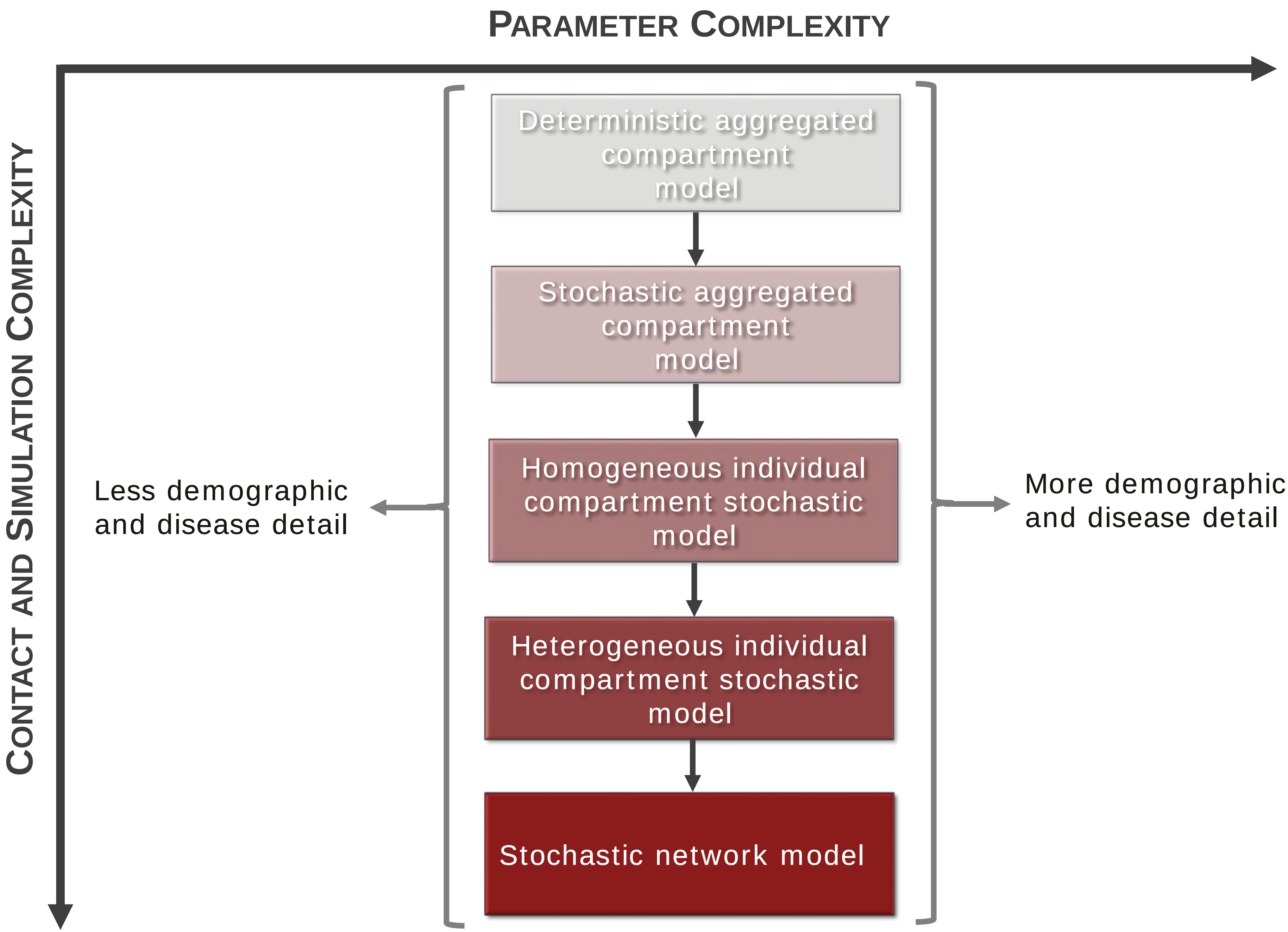
Methods (cont.)

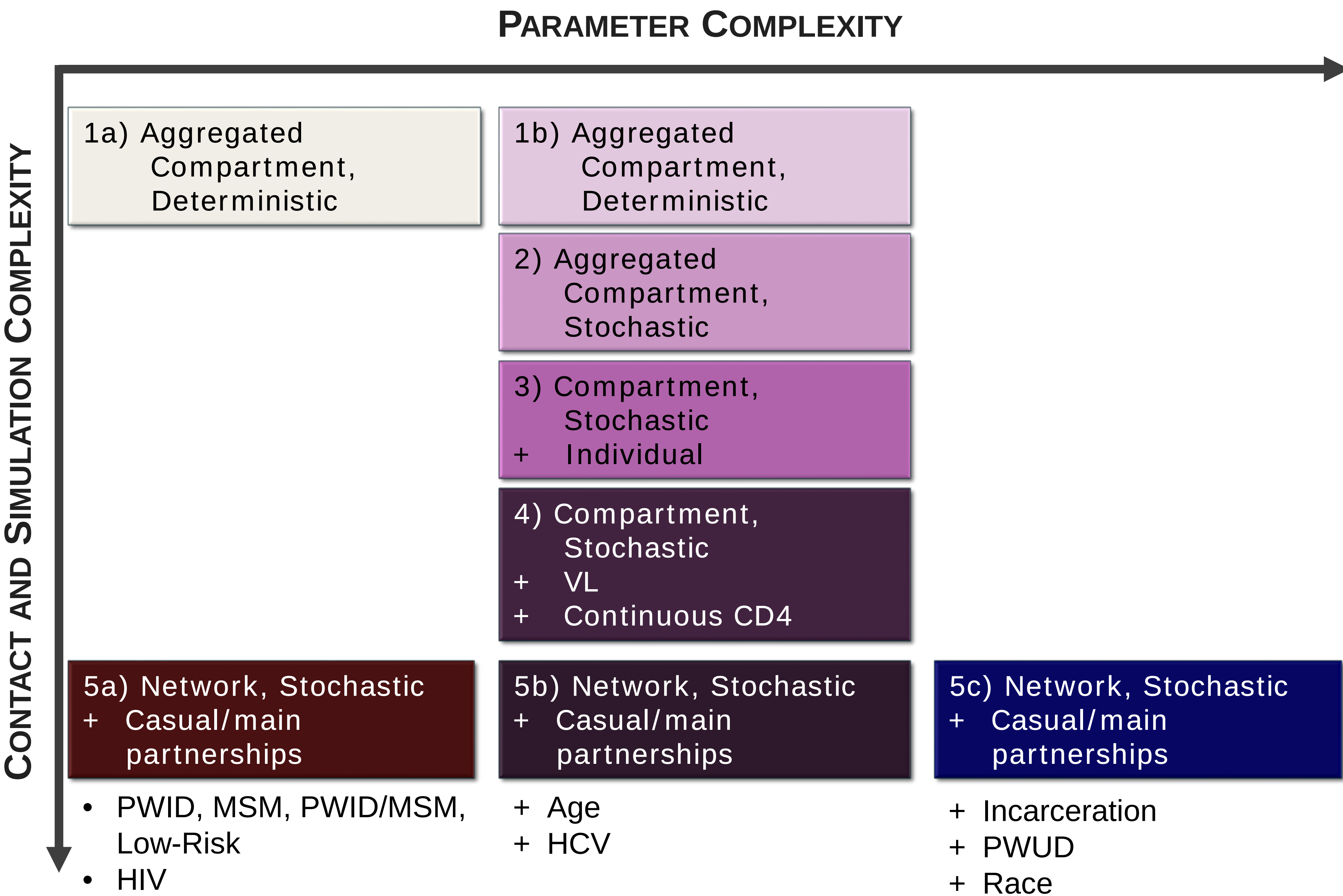
- Models implemented in Python (5 years, 1-month time step)
- Simulated 10% of King County population (140,000 people)

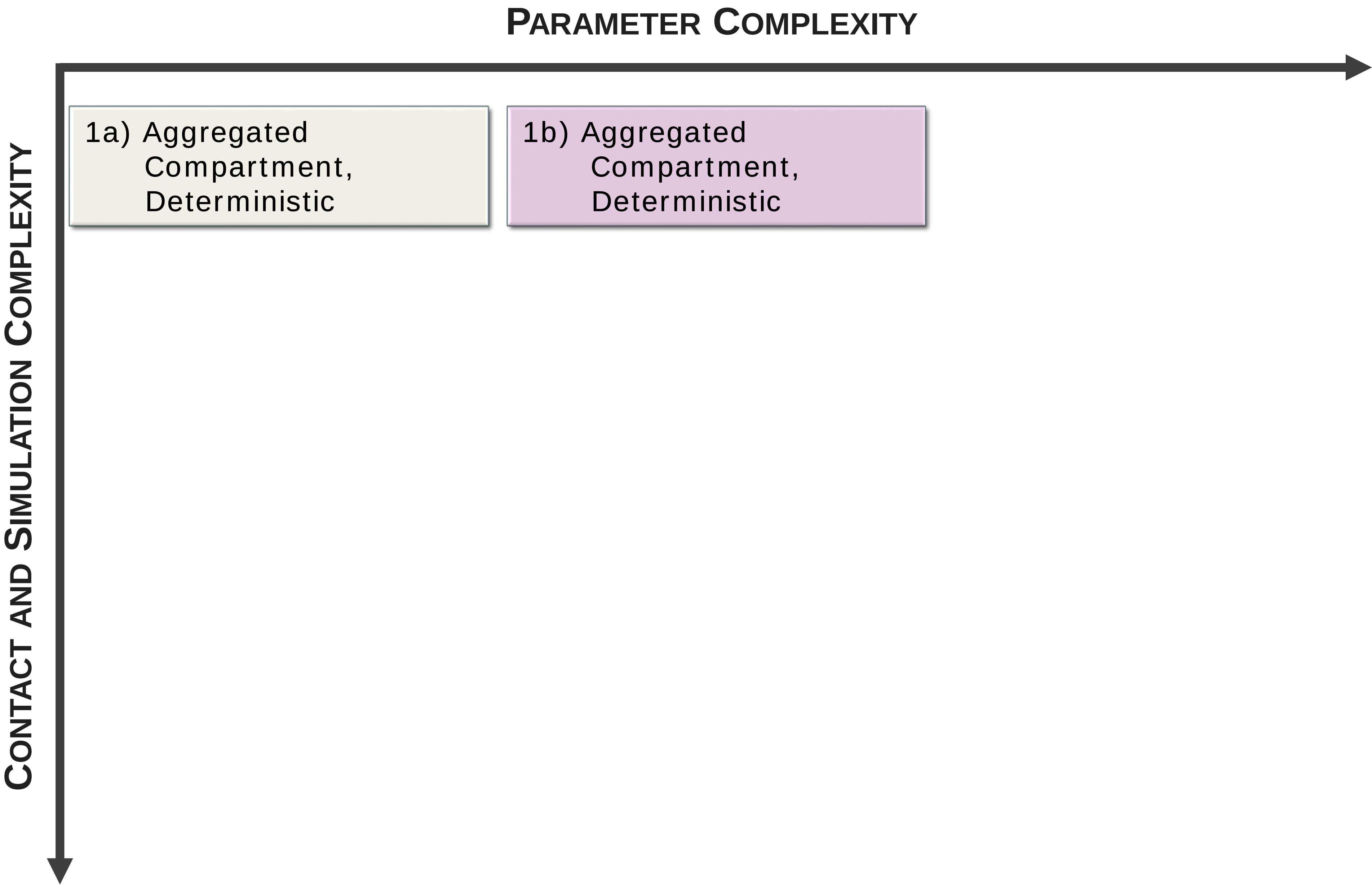
Low risk:	131,750
MSM:	5940
PWID:	2130
MSM/PWID:	180

- Hypothetical HIV vaccine
  - Efficacy (25%, 75%), coverage (25%, 100%), Cost ($300, $1000)

How do estimates of vaccine effects and cost-effectiveness differ across the models?


PARAMETER COMPLEXITY
CONTACT AND SIMULATION COMPLEXITY
Deterministic aggregated compartment model
Stochastic aggregated compartment model
Homogeneous individual compartment stochastic model
Heterogeneous individual compartment stochastic model
Stochastic network model
Less demographic and disease detail
More demographic and disease detail

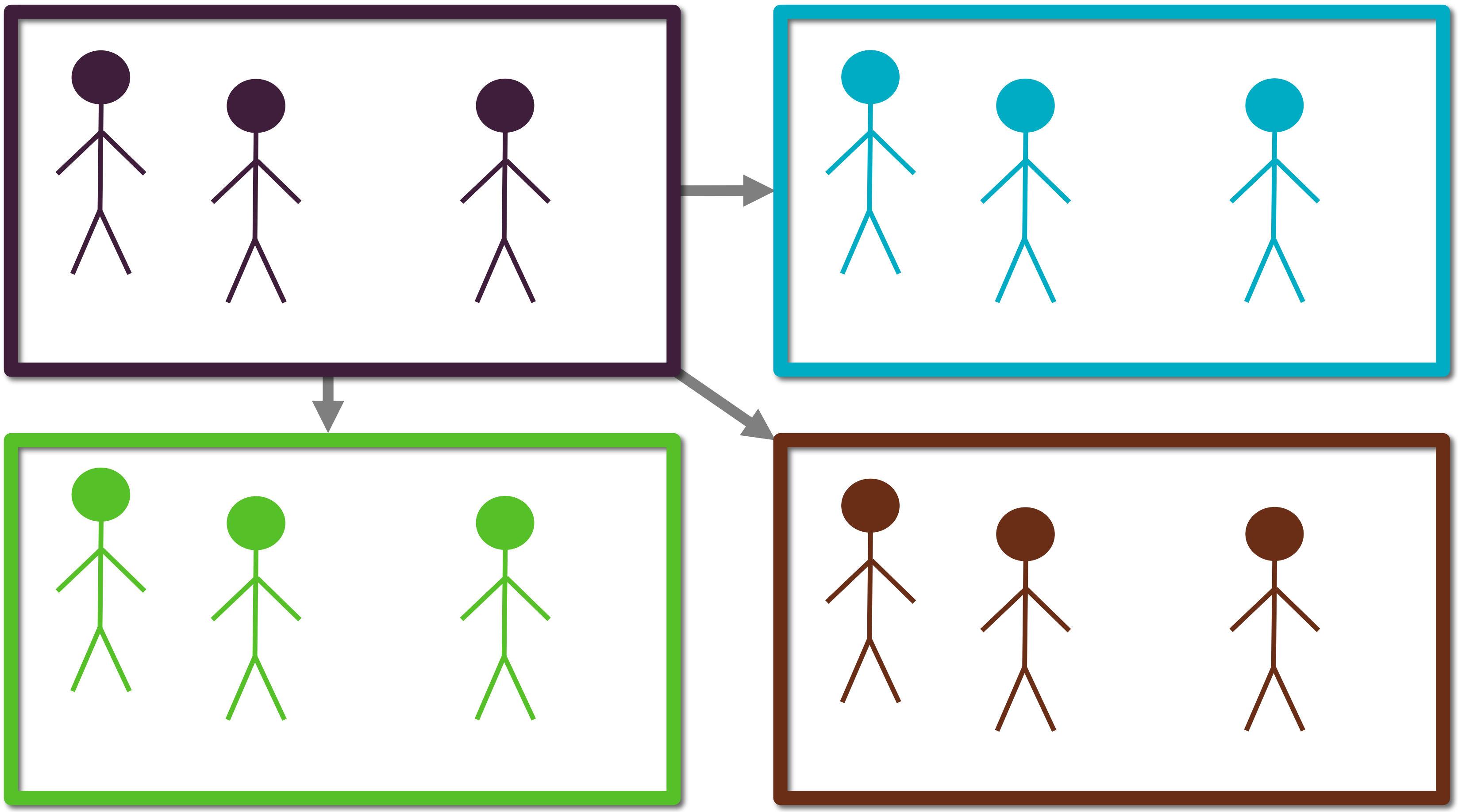

PARAMETER COMPLEXITY
CONTACT AND SIMULATION COMPLEXITY
1a) Aggregated Compartment, Deterministic
1b) Aggregated Compartment, Deterministic
2) Aggregated Compartment, Stochastic
3) Compartment, Stochastic
+ Individual
4) Compartment, Stochastic
+ VL
+ Continuous CD4
5a) Network, Stochastic
+ Casual/main partnerships
• PWID, MSM, PWID/MSM, Low-Risk
• HIV
5b) Network, Stochastic
+ Casual/main partnerships
+ Age
+ HCV
5c) Network, Stochastic
+ Casual/main partnerships
+ Incarceration
+ PWUD
+ Race



PARAMETER COMPLEXITY
CONTACT AND SIMULATION COMPLEXITY
1a) Aggregated Compartment, Deterministic
1b) Aggregated Compartment, Deterministic

Methods

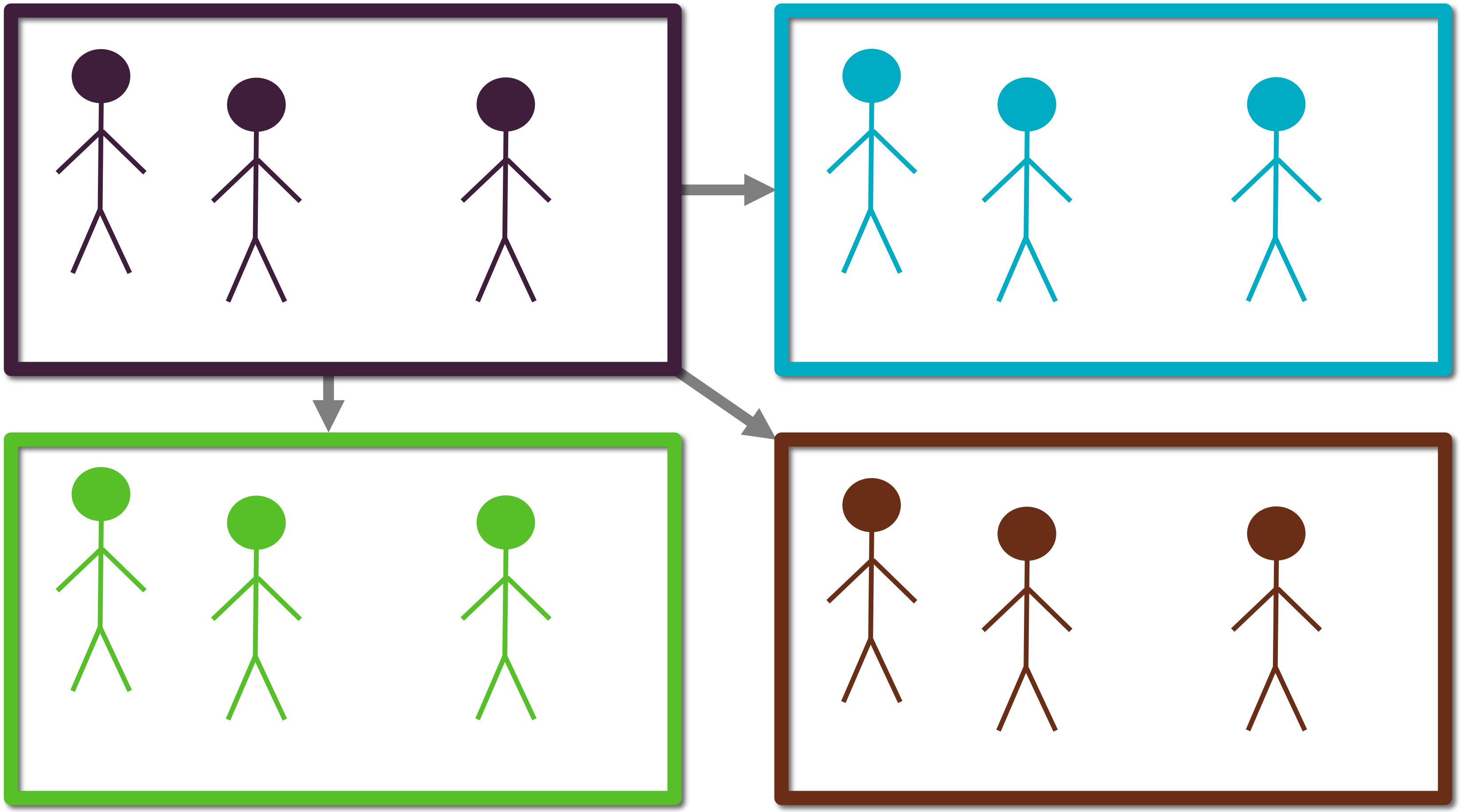
Model 1a: Aggregated Compartment, Deterministic



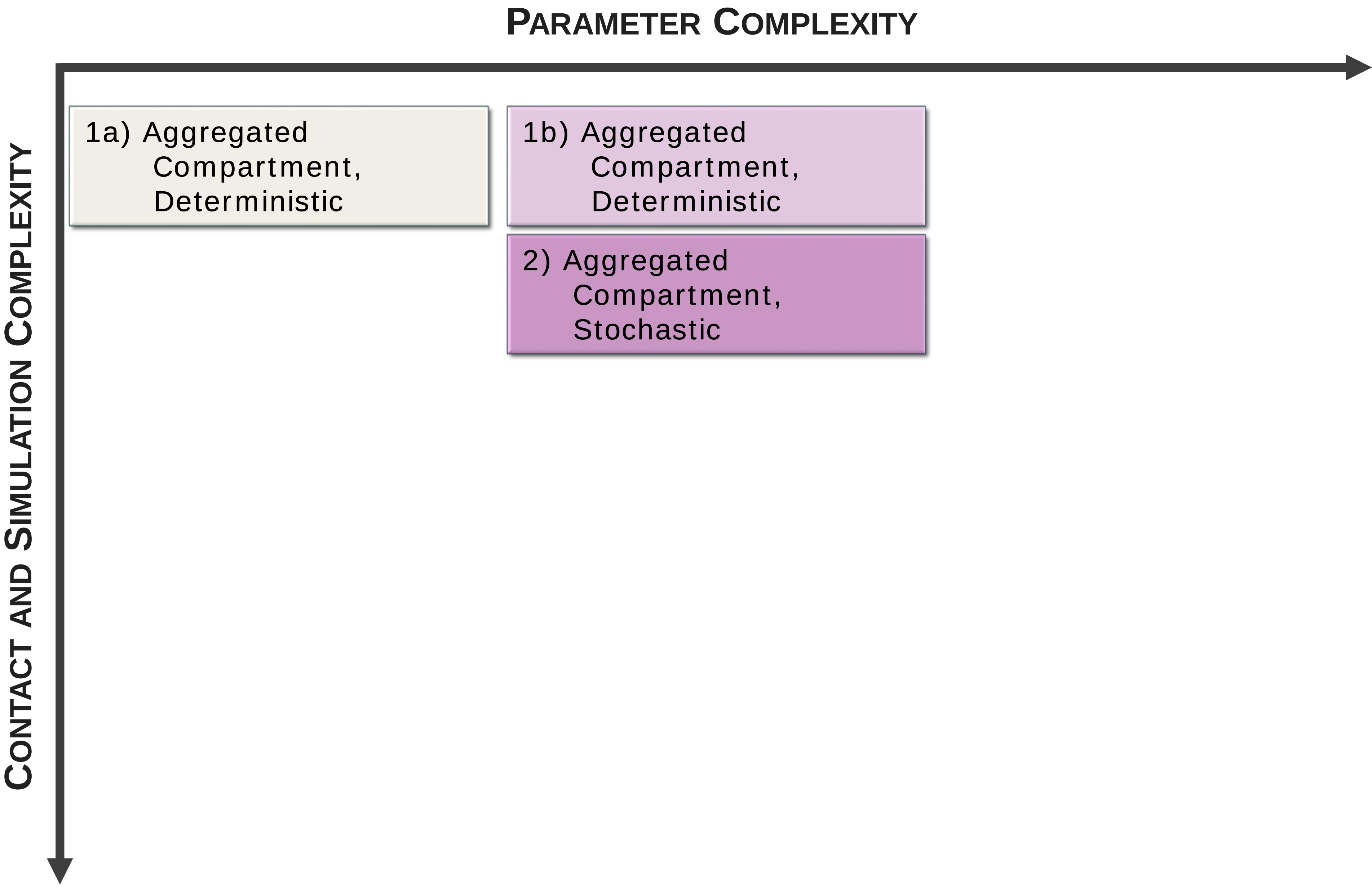
Four risk groups (compartments), HIV status

Methods

Model 1b: Aggregated Compartment, Deterministic



Add age structure, HCV status



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1a) Aggregated Compartment, Deterministic
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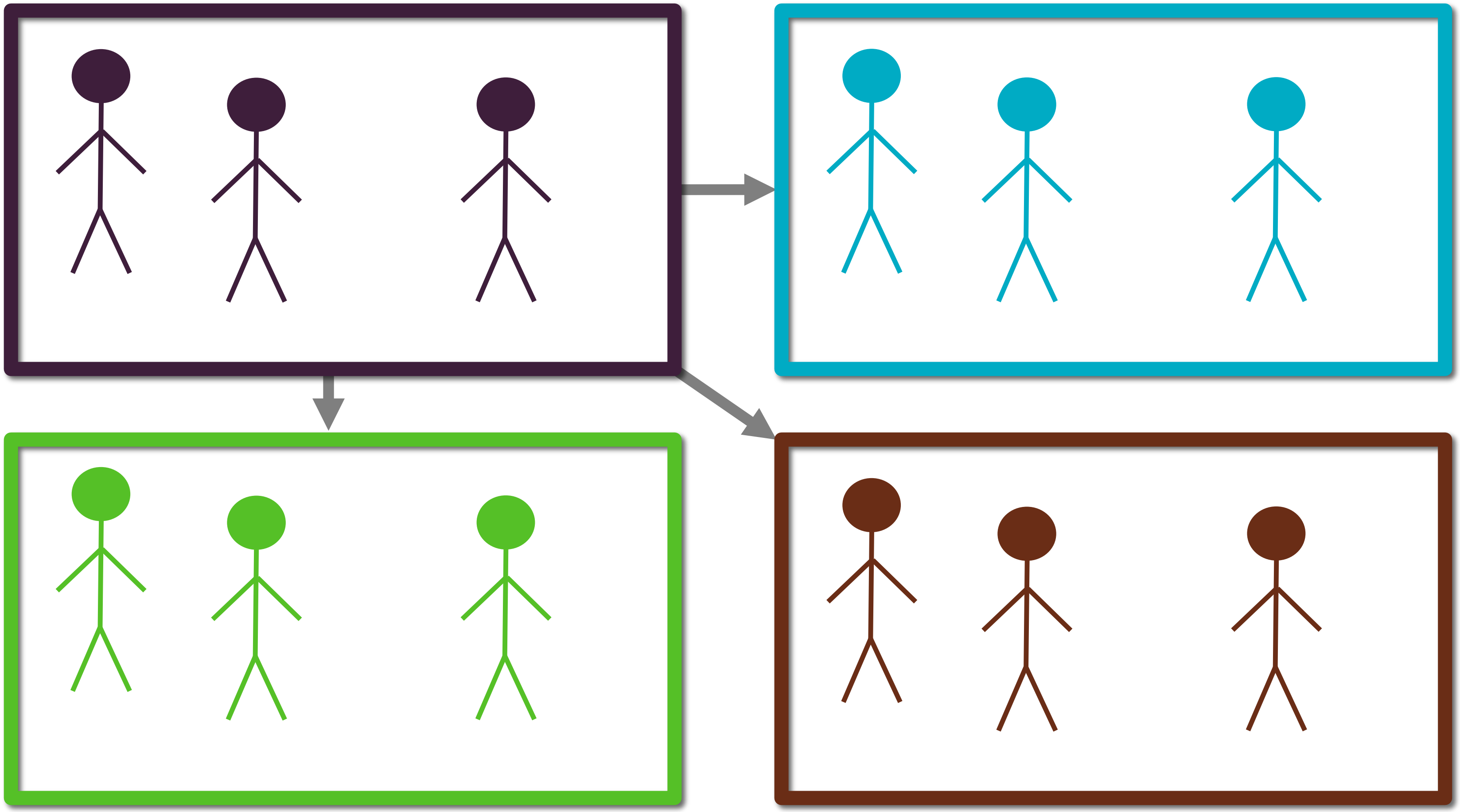
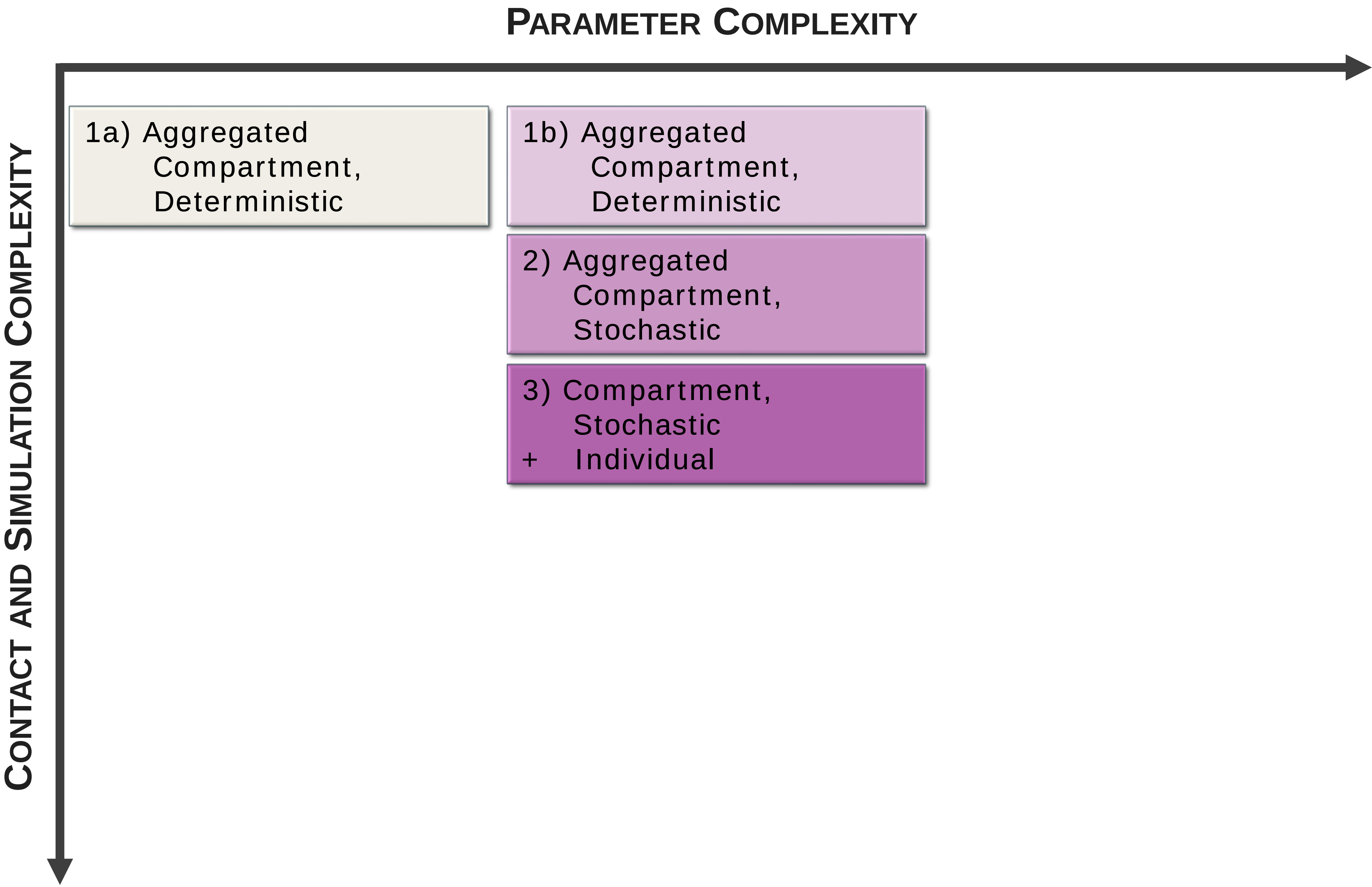
Methods

Model 2: Aggregated Compartment, Stochastic



Population demographics assigned stochastically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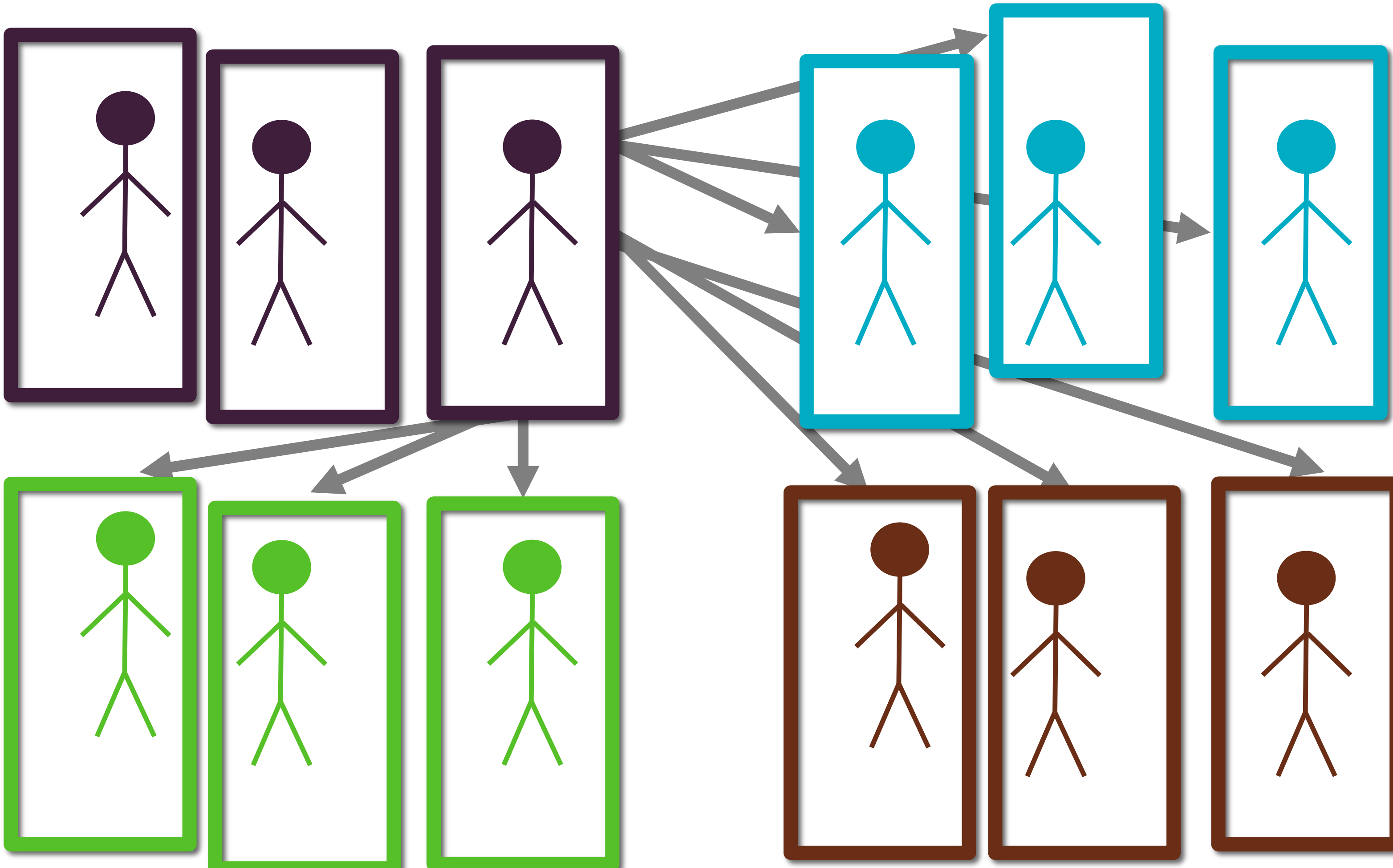
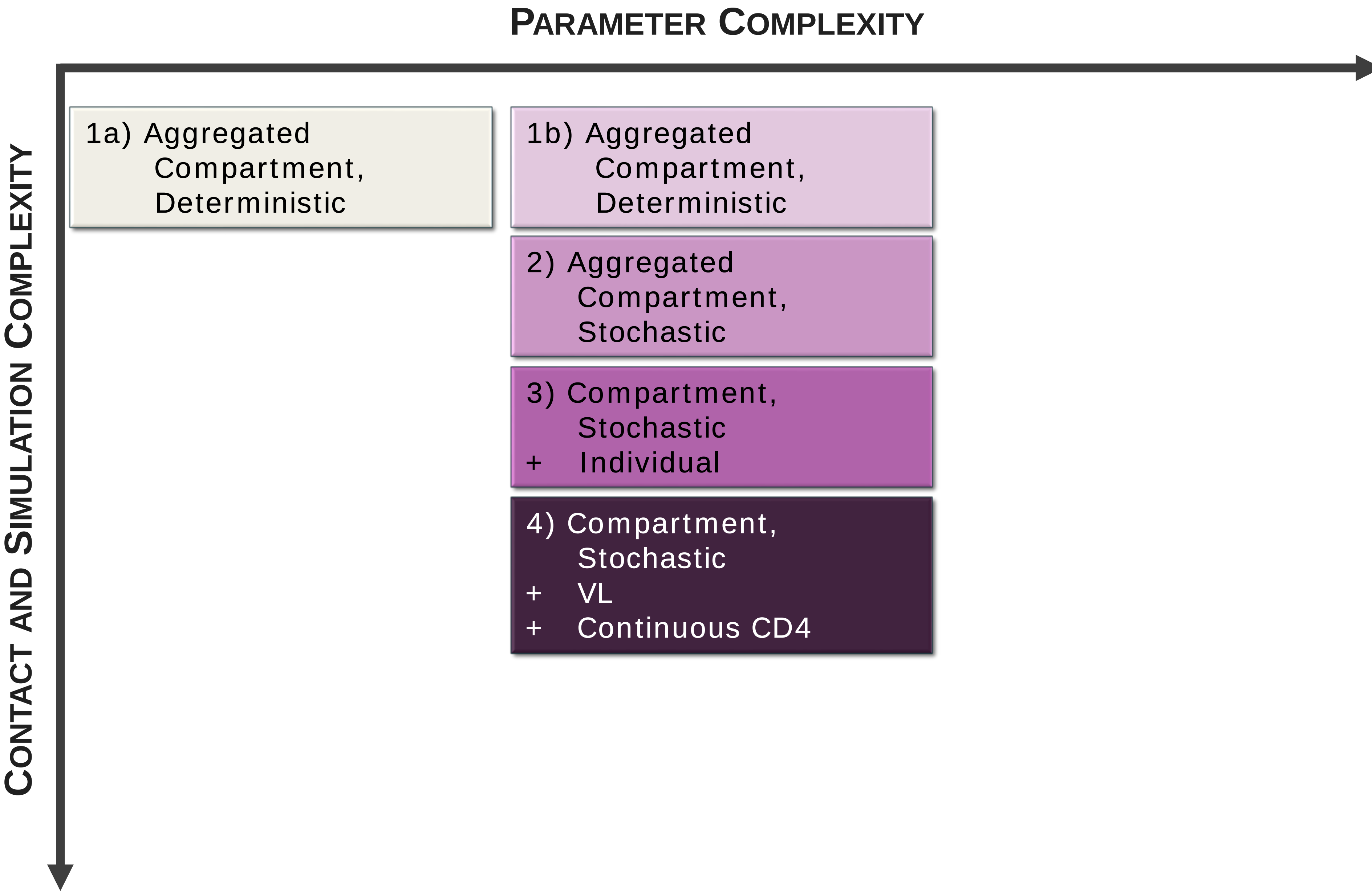
3) Compartment, Stochastic
+ Individual

Methods

Model 3: Compartment Stochastic, Individual



Individual compartment model with discrete-time stochastic simulation



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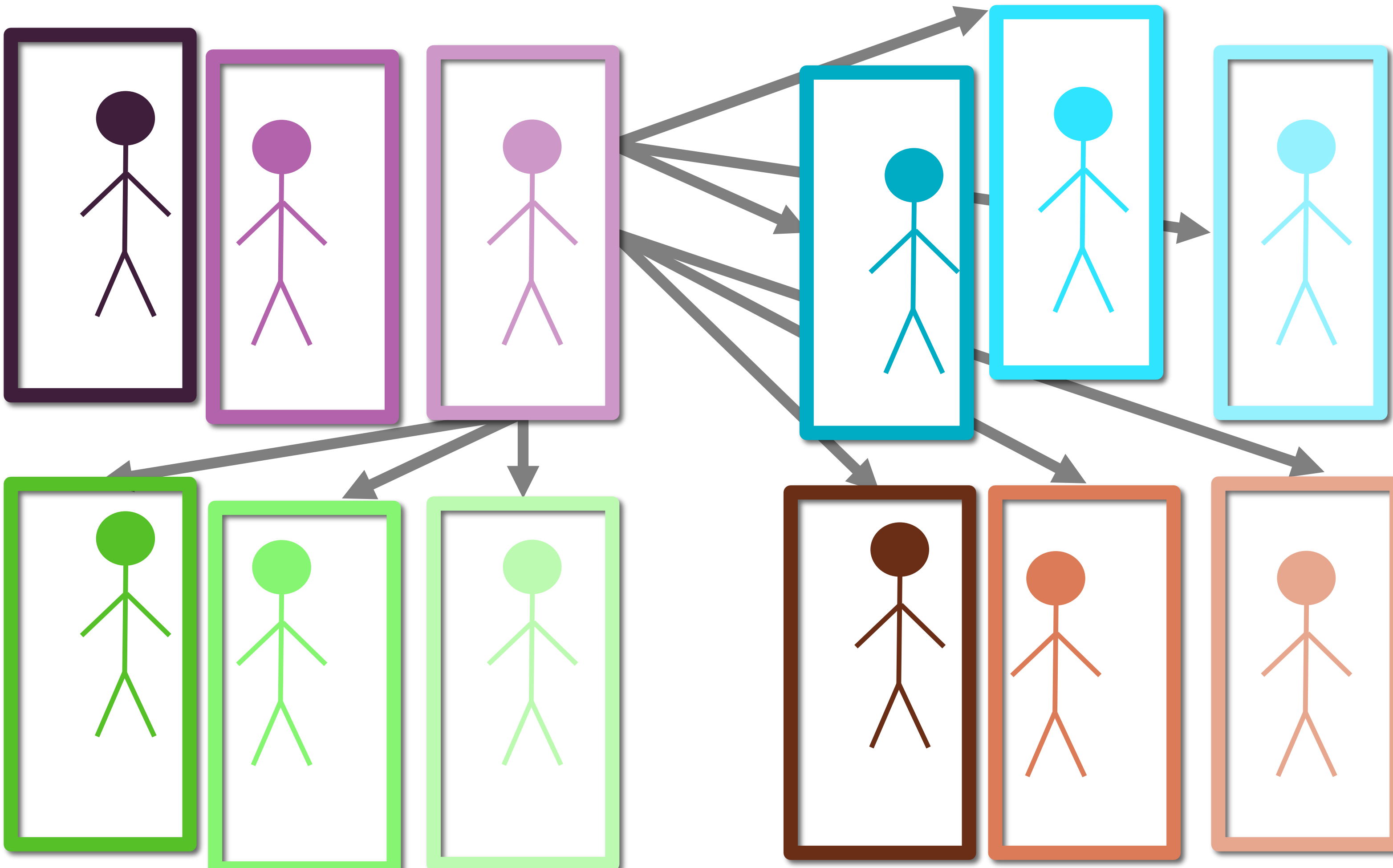
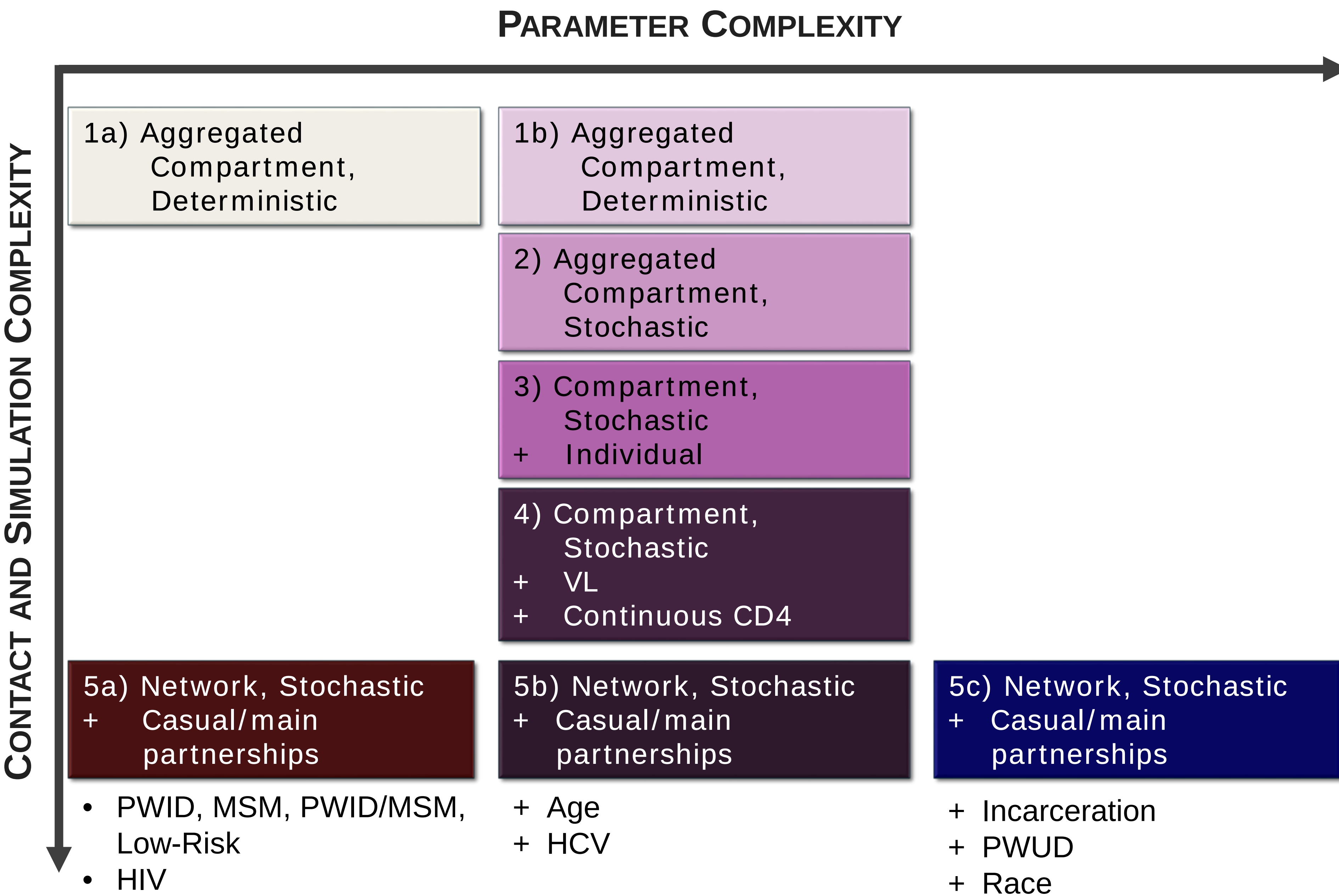
4) Compartment, Stochastic
+ VL
+ Continuous CD4

Methods

Model 4: Compartment, Stochastic, Individual Event History



Add individual event history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• HIV
5b) Network, Stochastic
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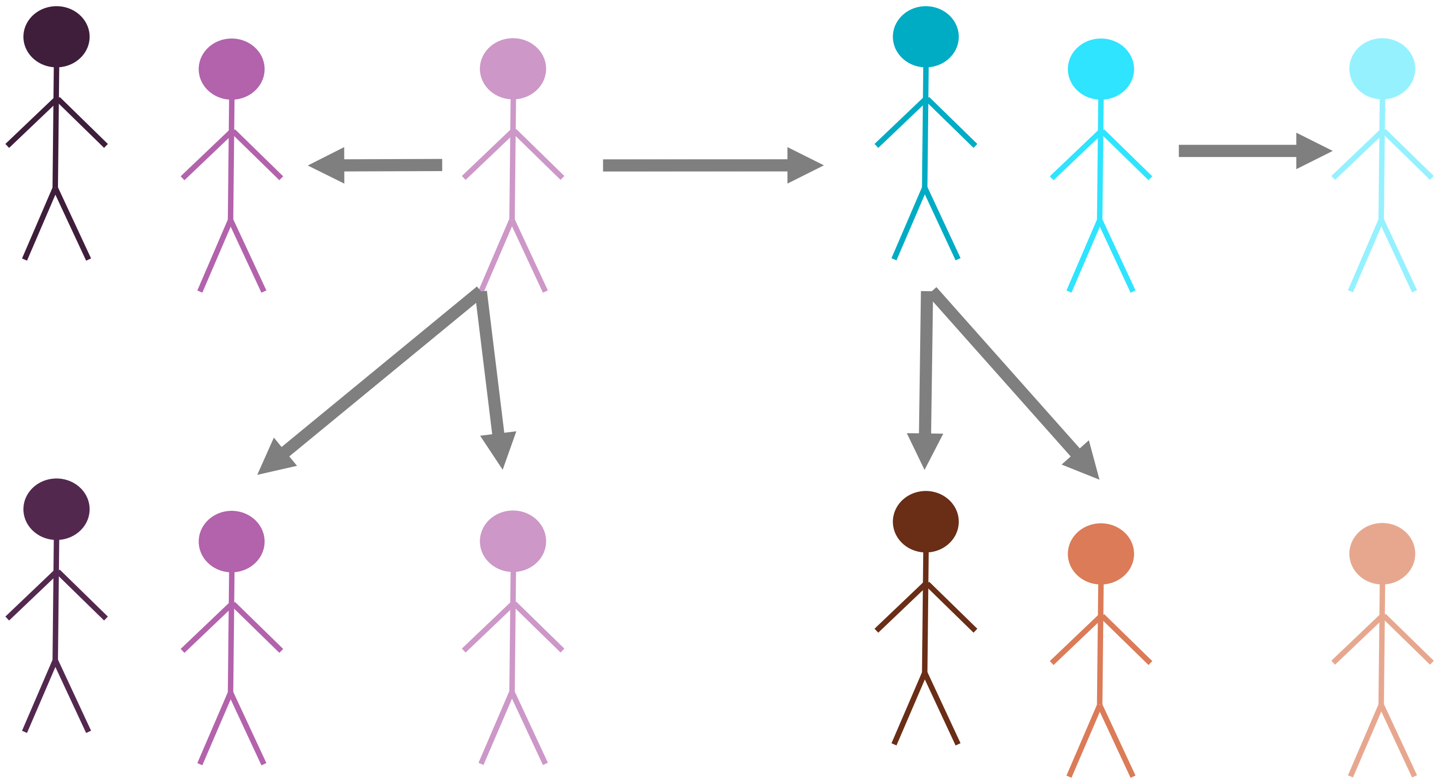
+ Age
+ HCV
5c) Network, Stochastic
+ Casual/main partnerships
+ Incarceration
+ PWUD
+ Race

Methods

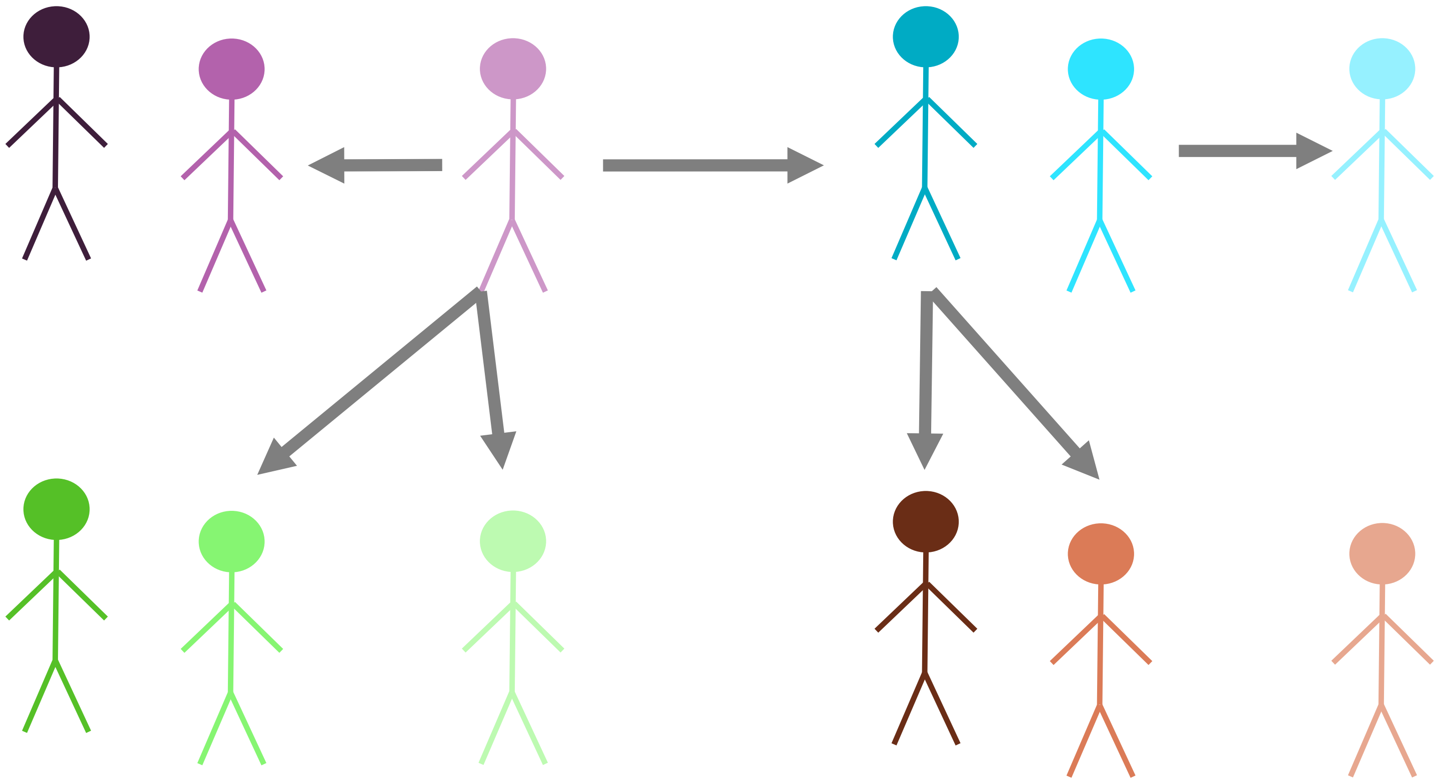
Model 5a: Network Simulation, Low Complexity



Network model with partnerships; consider only HIV status

Methods

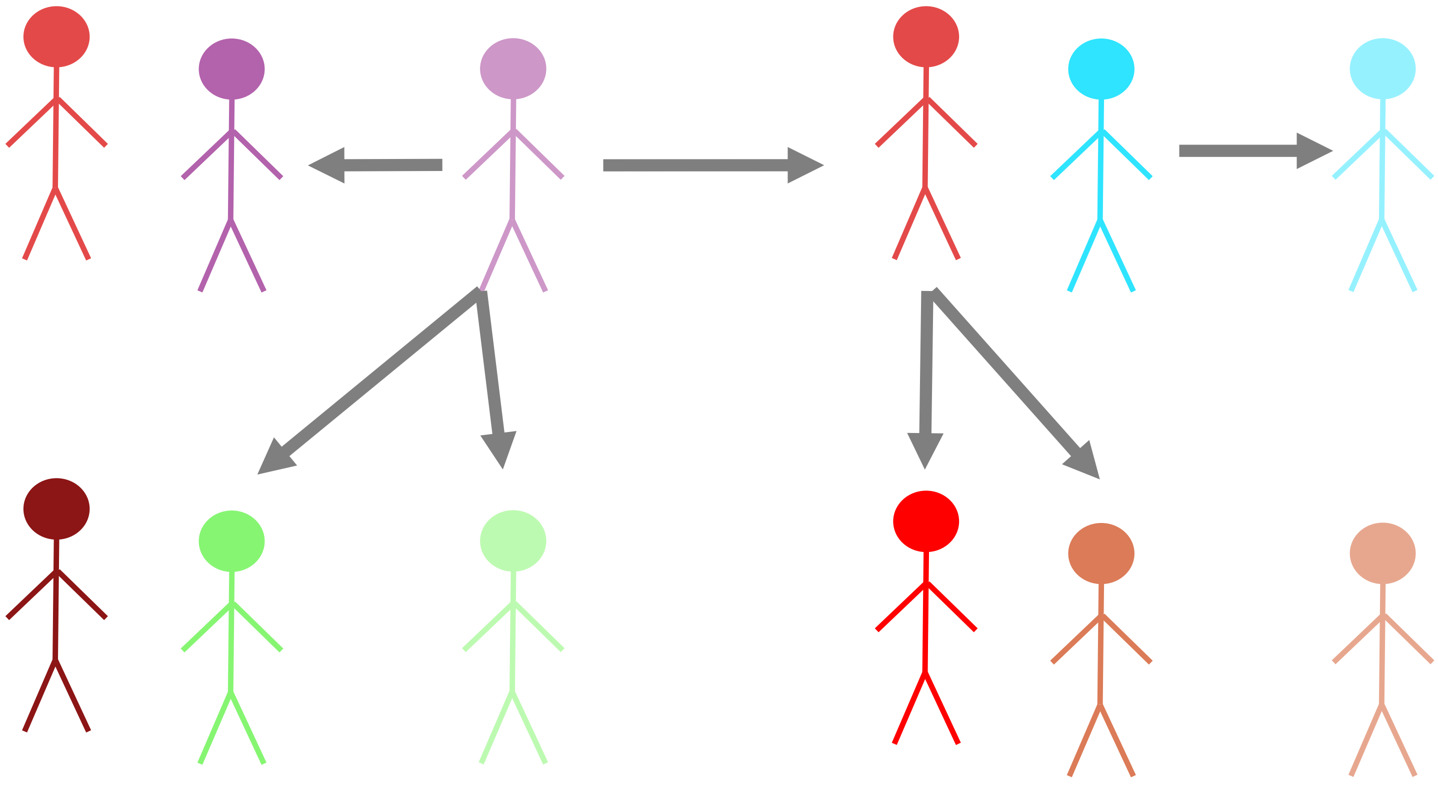
Model 5b: Network Simulation, Medium Complexity



Add age, HCV status

Methods

Model 5c: Network Simulation, High Complexity

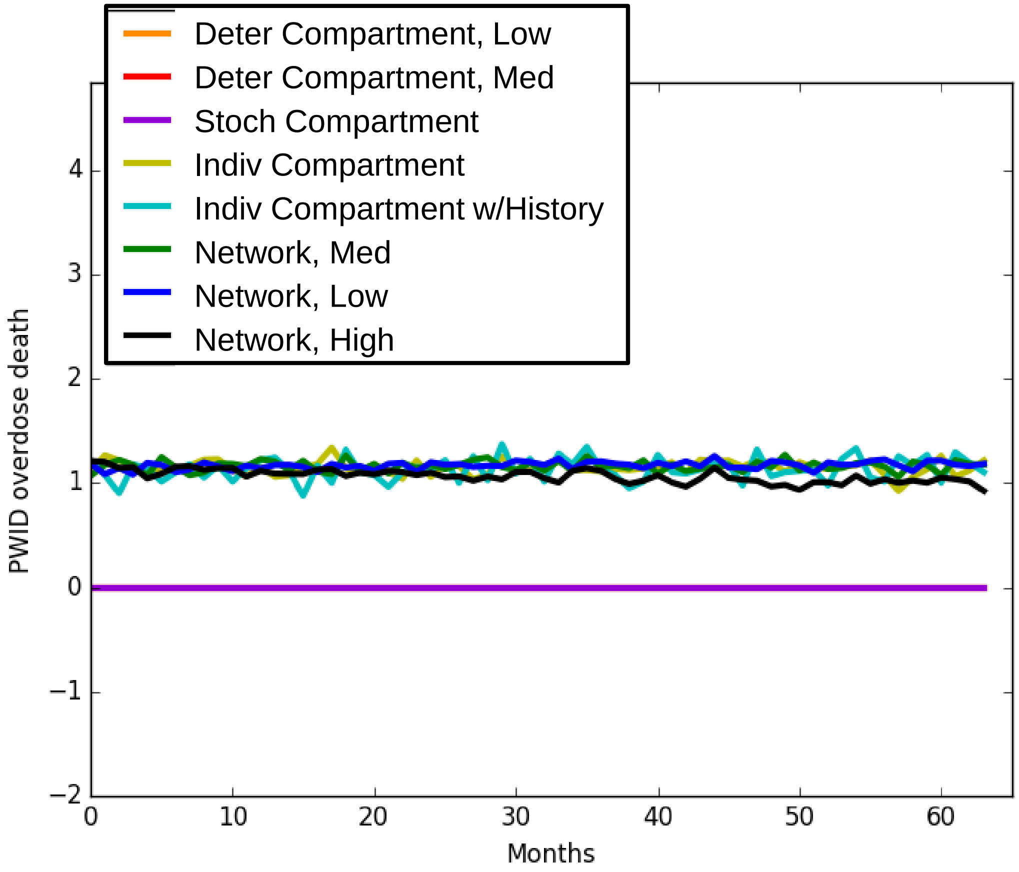


Add race, incarceration status, drug use status

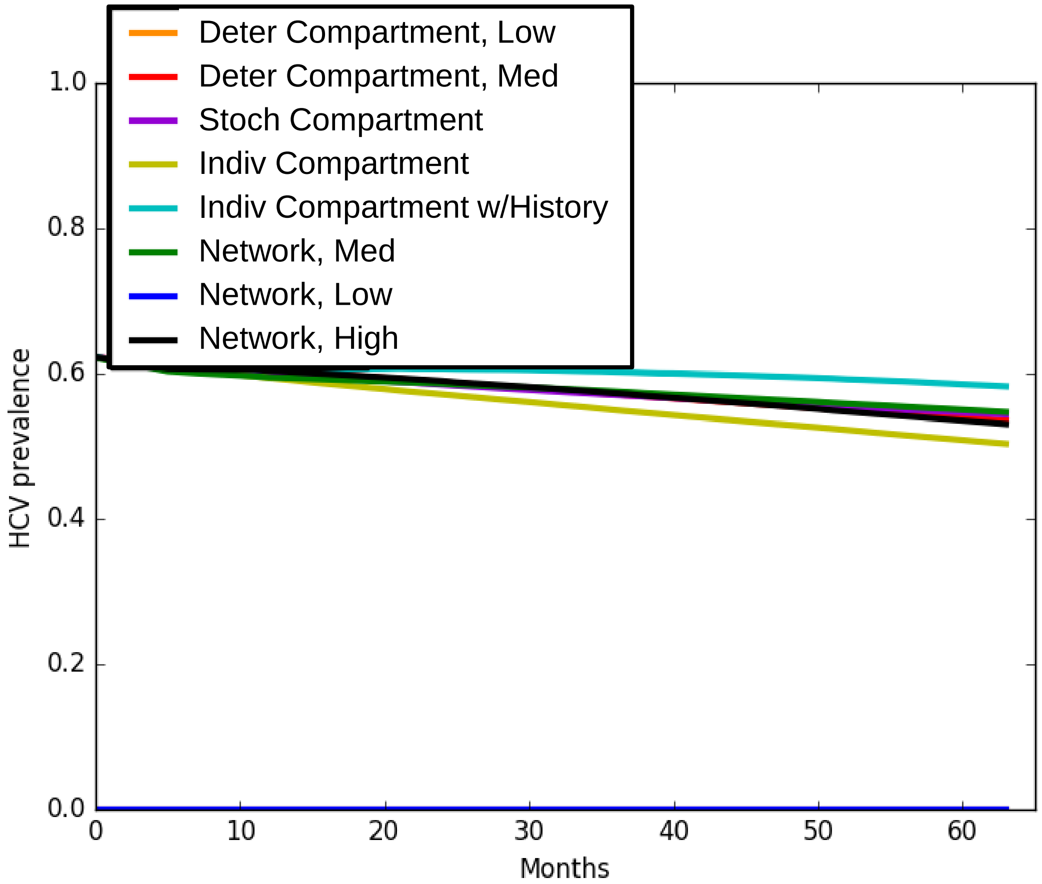
Model development

- Created the models from most to least complex
- Built Model 5c (stochastic network microsimulation)
- Calibrated it
- “Condensed” into Model 5b (eliminated incarceration, race, PWUD status)
- Moderate calibration
- “Condensed” into Model 4 (stochastic compartmental model with no explicit partnerships)
- Moderate calibration
- Etc.

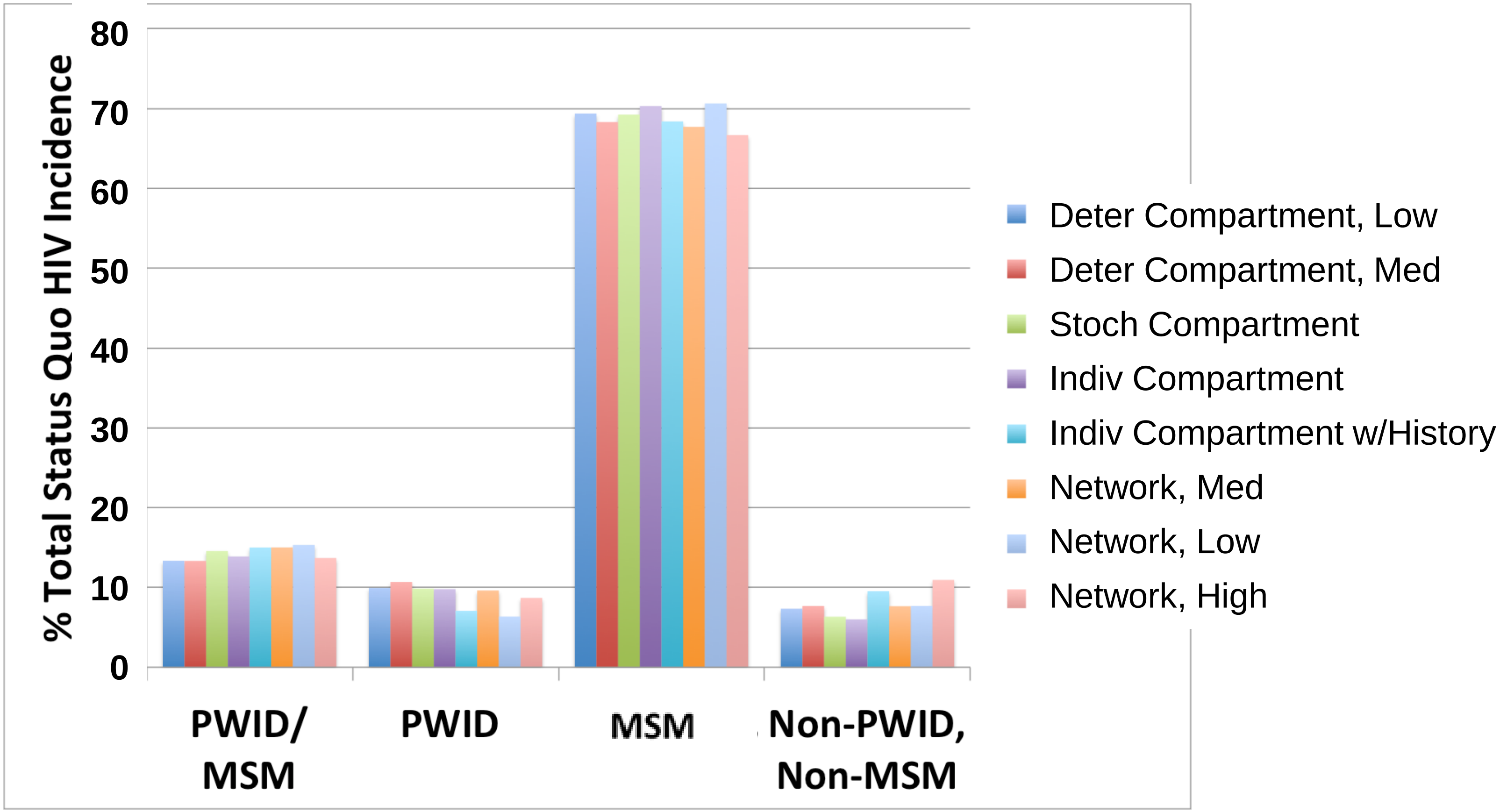
Calibration: overdose deaths



Calibration: HCV prevalence



Calibration: HIV incidence



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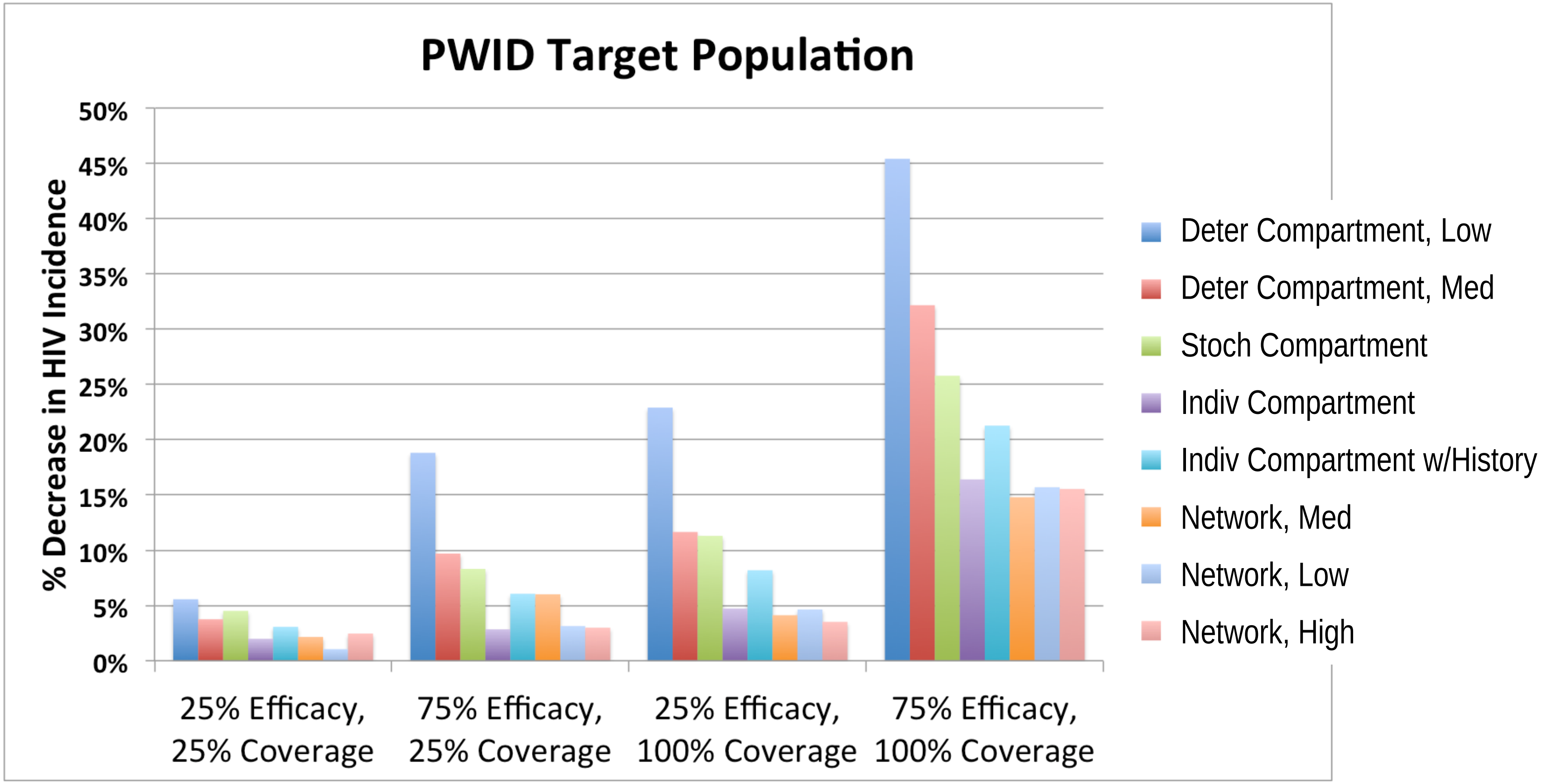
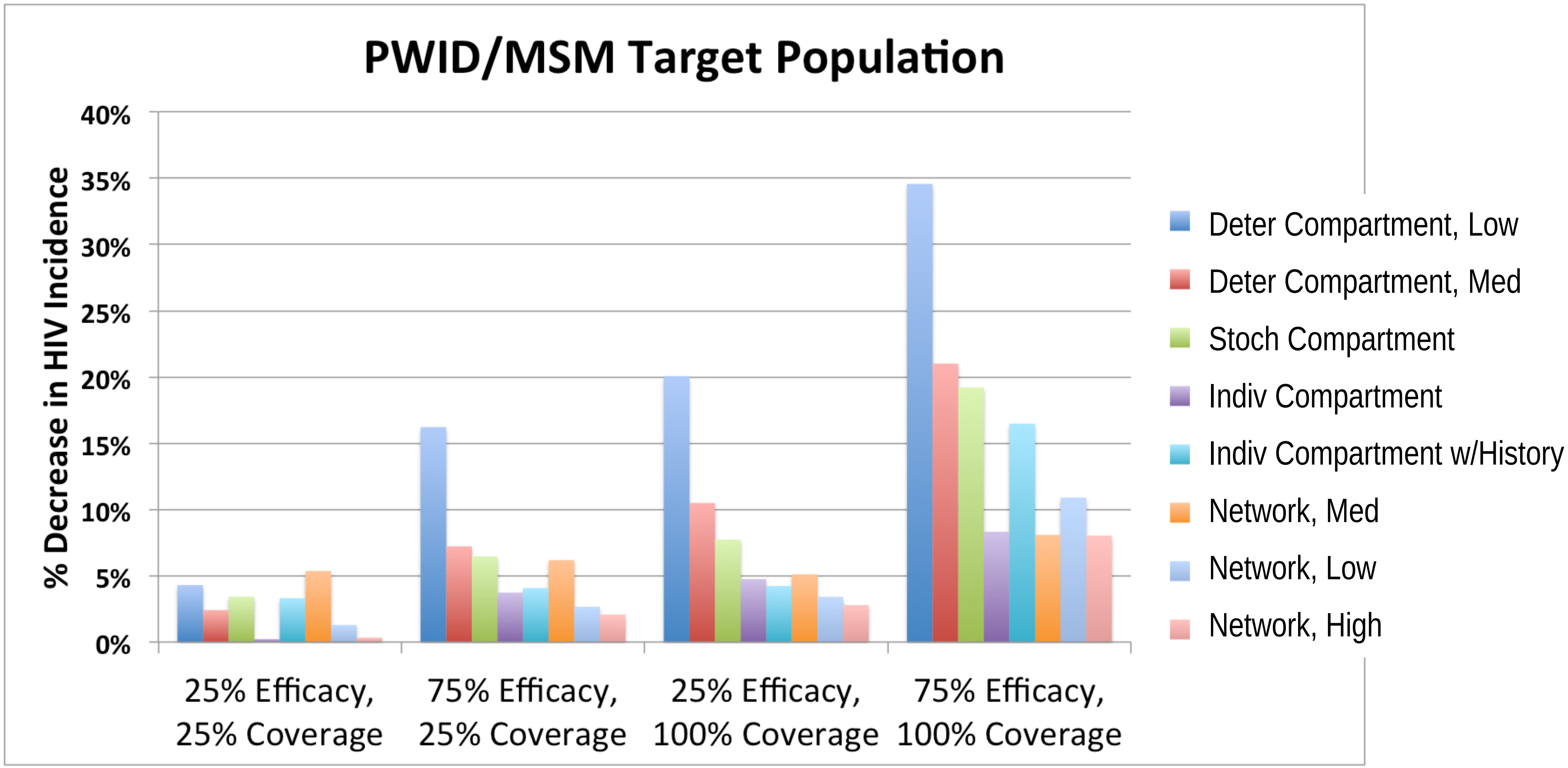
Results: Vaccine effectiveness



Aggregated models predict significantly larger vaccine effect

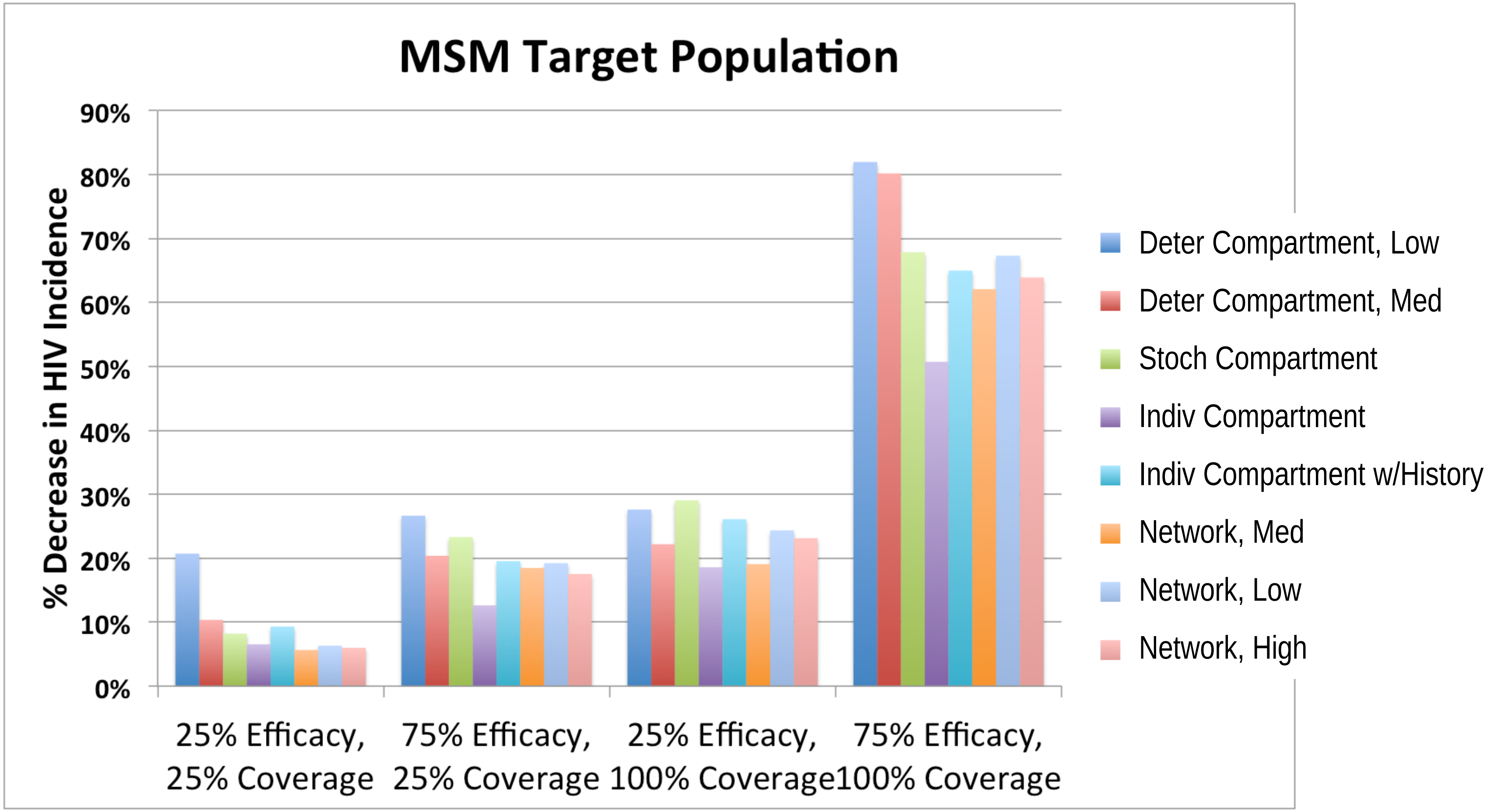
Effect is most pronounced for high coverage/efficacy

Results: Vaccine effectiveness



Effect of aggregation is more pronounced for small populations

Results: Vaccine effectiveness



Lesser difference for a larger population

Parameter complexity not important for disaggregated models

Results: Cost-effectiveness

	Deterministic Compartment, Low				Deterministic Compartment, Med			
Scenario	Fraction of HIV Infections Averted	Δ Costs ($1000)	Δ QALYs (1000)	ICER	Fraction of HIV Infections Averted	Δ Costs ($ 1000)	Δ QALYs (1000)	ICER
PWID: [L, H, L]	0.23	-1645	203	-$8,103	0.12	638	77	$8,286
PWID: [L, H, H]	0.23	120	203	$591	0.12	1935	77	$25,130
PWID: [H, H, H]	0.45	-337	362	-$931	0.32	2058	188	$10,947
MSM: [L, H, L]	0.28	-2565	243	-$10,512	0.22	-1804	166	-$10,867
MSM: [L, H, H]	0.28	-557	243	-$2,292	0.22	361	166	$2,175
MSM: [H, H, H]	0.82	-7018	743	-$9,445	0.80	-5712	664	-$8,602

Scenarios -- “target population: [vaccine efficacy, vaccine coverage, vaccine cost]”
L and H denote low or high
Vaccine efficacy [25%, 75%]; coverage [25%,100%]; cost [$300, $1000]

Parameter complexity makes a difference in Model 1

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Conclusions from case study

- Structural complexity
  - Aggregated models overestimate effect compared to individual models
  - Differences most pronounced in small populations and for higher intervention effectiveness
  - Threshold for use of aggregated models?
- Parameter complexity
  - Makes a difference in aggregated compartmental models
  - Less so for network models

Further work

- Results are illustrative, not prescriptive
- Comparative model simulation is the first step…
- Useful to focus on aggregated vs. disaggregated compartment models (Models 2 and 3)
  - Further inference robustness assessment
  - Simple analytic exploration

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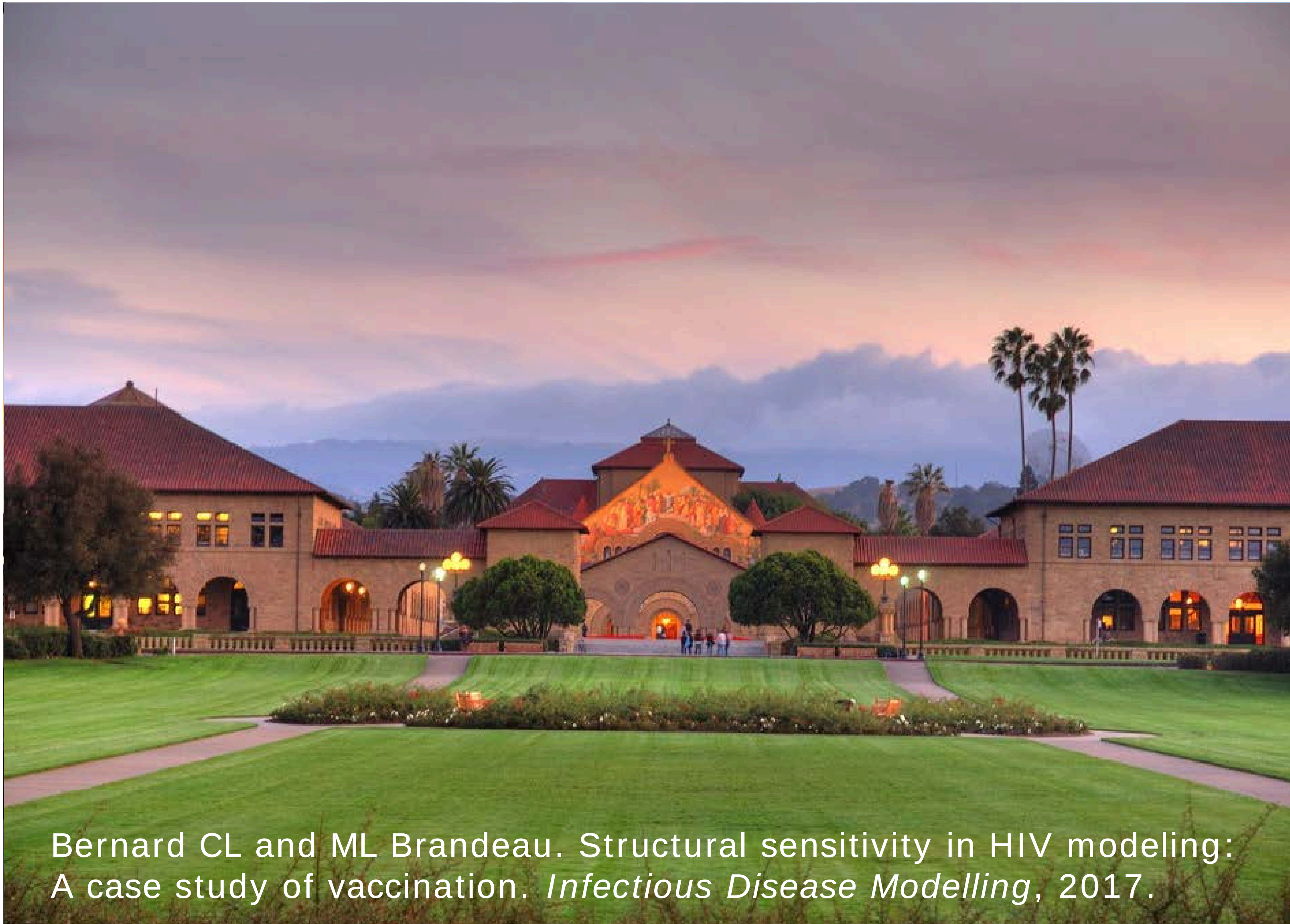
Final thoughts

- Structural assumptions in models of stochastic processes can significantly affect policy conclusions
- When building a model, need to be thoughtful – and explicit – about assumptions
- Data may be a limiting factor
- We should expand our notion of sensitivity analysis
  - Build models that can turn on/off elements of stochastic complexity
- VOI $\rightarrow$ VOC?
- Policy modelers could benefit from more communication with stochastics experts

Thank you



Bernard CL and ML Brandeau. Structural sensitivity in HIV modeling: A case study of vaccination. *Infectious Disease Modelling*, 2017.