How Sensitive are My Conclusions to Model Assumptions: Insights from Health Care Models

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October 2004

Type of Model

- "keeping models simple enhances understandability and theoretical utility but that using models for disease control decisions often requires realism that adds considerable complexity."
  – Roy Anderson

Factors for choosing a model

- *Why Patient Level Simulation?*
  - *Need patient-level information from model*
  - *Sufficiently heterogeneous populations (many risk groups, many stages of natural history, geography)*
  - *Constrained resources (queuing and health outcome)*
  - *Patient interaction (e.g. infectious disease transmission)*
- *Purpose: understand one system (sensitivity) or select best of finite set or optimize*
- *Estimand: Mean? Variance? Distribution?*

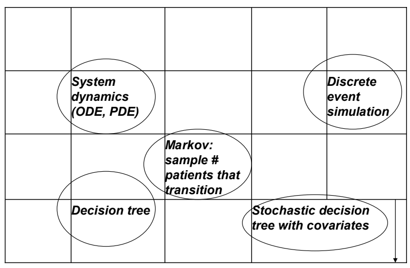
Factors for choosing a model

- *Also:*
  - *Stationary versus transient*
  - *Time invariant versus time varying parameters*
  - *Continuous time versus discrete time versus untimed*
  - *Deterministic versus stochastic*
  - *Large or small population*
- *The simplest model to answer a question is preferred (Occam's razor)*
- *Different model types can give different conclusions*
- *Goal: Understand how models relate, and what systematic implications are due to model choice*

Roadmap

- ***Model Type***
  - ***System dynamics; Markov chain; discrete event simulation at patient level***
- *Independence and system dynamics*
  - *Water treatment policy for the E.P.A.*
- *Stochastic versus deterministic*
  - *Infectious disease control: NTHi*
- *Patient-level, discrete-event simulations*
  - *Structure, time-oriented social dynamics, resource constraints*
- *Call for model transition sensitivity analysis*
  - *Open Questions*

Some Models



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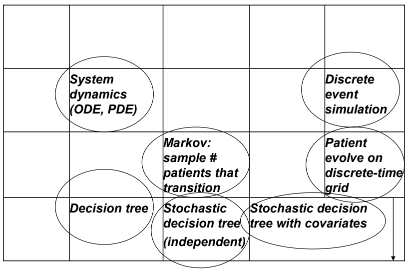
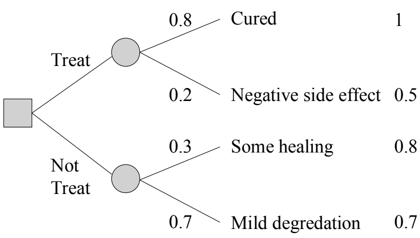


Model Hierarchy

	Aggregate level		Patient level	
	Deterministic continuous state	*Stochastic discrete counts*	*Stochastic Markovian individual*	*Stochastic general distribution individuals*
Continuous time	*System dynamics (ODE, PDE)*	*Stochastic Markov model (queue,…)*	*Patient-level simulation (interact)*	*Discrete event simulation*
Discrete time	*Finite difference model*	*Markov: sample # patients that transition*	*…*	*Patient evolve on discrete-time grid*
Untimed	*Decision tree*	*Stochastic decision tree*	*Stochastic decision tree with covariates*	

Decision Tree



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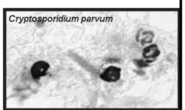
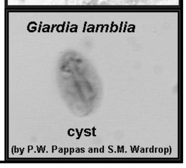
Waterborne Transmission of Infection and Risk of Infectious Disease

- Chemical risk versus Microbial risk
- Public health issue.
  - Crypto, giardia, legionella, …
  - CCL: adeno- & caliciviruses, MAC, …
  - Outbreak! Two of many…
    - Milwaukee, Crypto, 1993: 400 000 w/ diarrhea; 1 000 ⇒ hospital; 53 died (HIV)
    - Walkerton, Ontario, E. coli O157:H7, 2001: 2 000 ill; 7 died
  - Endemic: May be more significant!





Microbial Risk Assessment

- Similarity with chemical risk
  - Primary exposure: exogenous source
- Standard approach
  - Identify hazards
  - Quantify occurrence and exposure
  - Assess dose-response relationship
  - Identify human health effects
- But…
  - Exposure to microbes from secondary transmission depends on number of infected individuals
    - Human to human
    - Human to environment to human

Comparative Analysis: Milwaukee in Retrospect

- HIV community more susceptible? Did suffer more serious outcomes
- Chemical Risk: Filter (local) vs. Ozone (global)
  - Contaminated water $\Rightarrow$ exposure to HIV community
  - $100 Million question
  - Assessment: Filters 10x more effective than ozone
- Microbes: Secondary transmission
  - Even with 100% effective filters, human-human transmission might continue infection!
  - Can ozone be more effective than filters?

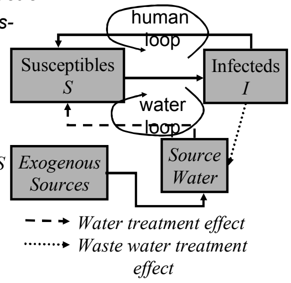
Simplified Transmission System: ODE Infection Transmission Model

- *Natural history of infection*
  - *Susceptible-Infectious-Susceptible (SIS)*
- *Infection dynamics*

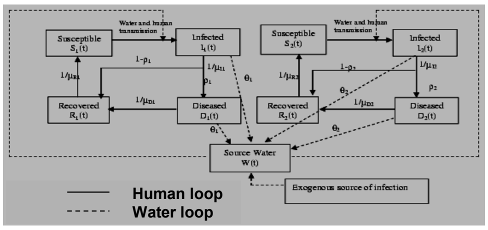
$$\frac{dS}{dt} = -(\text{direct} + \text{indirect}) + \text{recovery} = -r\phi WS - c\beta\frac{I}{S+I}S + \frac{I}{D}$$

- *Water contamination*

$$\frac{dW}{dt} = \gamma + \theta I - \alpha W$$



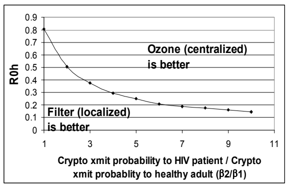
SIDRS-W model for Heterogeneous Populations



- More complex natural history of infection
- Subpopulations
- Human-human & human-water-human loops

Ozone/Filter Policy Regions

- *Ozone pretreatment: centralized, entire population*
- *Filters: targeted, in homes of HIV subpopulation*
- *Criterion: "better" = fewer crypto infections in HIV subpopulation*



R0h = mean number secondary transmissions from human contact

Summary: Independence and System Dynamics

- *Current U.S. water treatment policy for microbes based on invalid risk assessment*
- *Lives of many and hundreds of millions of £¥$€*
- *Dynamics of risk account for dependent outcomes*
- *One issue: Unknown transmission parameters*
- *System dynamics (aka ODE or PDE or compartmental models) embody risk dynamics*
- *Question: Are conclusions sensitive to the type of model (ODE versus stochastic dynamics)?*

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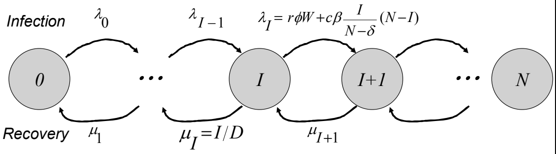
ODE ⇔ Markov Chain

$$\frac{dI}{dt} = -\frac{I}{D} + r\varphi W + c\beta \frac{I}{N}(N - I)$$

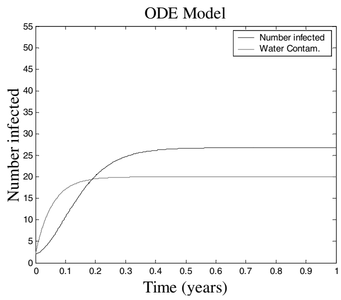
- *Realistic variability*
- *Large population*

	I	*S*
I	$1-\frac{1}{D}\Delta t$	$\frac{1}{D}\Delta t$
S	$\left(r\varphi W + c\beta\frac{I}{N}\right)\Delta t$	$1-\left(r\varphi W + c\beta\frac{I}{N}\right)\Delta t$



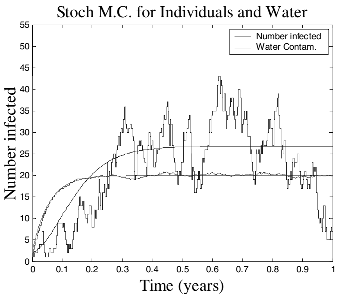
ODE Compartmental Models

- *Many have unique attractor*



Markov chain on lattice

- *"Shadow": count # individuals (people, microbes) in compartment.*



- *Apparent risk of local die-out of infection*

Pushing the model: Local and disseminating contact

- *Different agents transmitted differently*
- *Local:*
  - *Family unit, classroom, small office, geographic "word of mouth"*
- *Disseminating:*
  - *Contaminate source water, random mixing in street, "mass marketing"*
- *What if we have 2 groups, and vary the fraction of "local" contacts?*

ODE and MC give different mean prevalence if…

- *…most contacts are local*

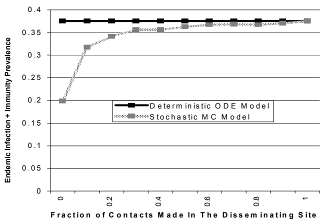
$$\frac{dI_1}{dt} = -\rho I_1 + c\beta S_1\left[f\frac{I_1}{N_1} + (1-f)\frac{I_1+I_2}{N_1+N_2}\right]$$

$$\frac{dI_2}{dt} = -\rho I_2 + c\beta S_2\left[f\frac{I_2}{N_2} + (1-f)\frac{I_1+I_2}{N_1+N_2}\right]$$

$$S_1 = N_1 - I_1$$

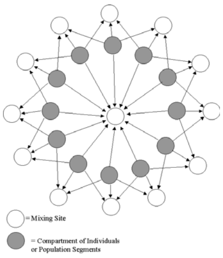
$$S_2 = N_2 - I_2$$

$$N_1 = N_2$$



ODE and MC give different mean prevalence if…

- *…or local groups are small*
- *Proof: Math Biosci 2002*



# per subgroup	Fraction of local contacts 0.0	0.25	0.50	0.75	0.90
ODE (∞)	0.500	0.500	0.500	0.500	0.500
MC 10	0.460	0.458	0.451	0.432	0.391
MC 20	0.483	0.483	0.481	0.473	0.462
MC 50	0.495	0.494	0.493	0.492	0.490

Summary: Stochastic versus deterministic model types

- *ODE: large population limit of MC for some models*
  - *(Ethier and Kurtz, Whitt, …)*
- *MC behavior differs on two levels*
  - *Random outcomes*
  - *Long-run averages may differ! (Local die-out of infection).*
- *Prevention:*
  - *Disseminating: municipal water treatment, SARS masks*
  - *Local: hygiene in families,behavioral*
  - *10% decrease in disseminating transmission reduces prevalence more than at 10% decrease in local*
  - *Vaccination: target to individuals ⇒ hits both local & global*

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How Sensitive are the Conclusions to the Assumptions?

- ***Partnership Concurrency and STDs***
  - *ODE models typically assume one long-term partner, several independent point contacts (e.g. Dietz, …)*
  - *Prevalence depends strongly upon potential of multiple longer-term partners (Adams Chick Koopman, Math Biosci 2000)*
- ***Smallpox preparedness***
  - *ODE says mass vaccination more effective than contact tracing, model with service capacity constraint (Kaplan, et al. PNAS 2002)*
  - *Patient-level simulation with social structures (family, neighborhood), richer natural history of infection implies surveillance, tracing about as effective (Longini et al. 2002, capacity,vaccine sequelae)*
- ***Local versus disseminating***
  - *Critical fraction of 'random contacts' leads to infection outcomes that are more similar to random mixing versus (Soorapanth, Chick Koopman 2001; social networks)*
- ***Service constraints and delays***
  - *Breast cancer screening not as sensitive to delays in a stochastic system as to other effects of service delivery program (outreach; frequency of screens; quality/volume, Gunes et al. HCMS 2004) – an ODE is sufficient*

Summary: Patient-level models

- *Outcomes and conclusions may depend upon the type of model, not just to input parameters*
- *Many patient-level models are 'black boxes', little information given for verification*
  - *No names given/no blame/ too many 'special cases'*
  - *Reasonable values if assumptions simplified?*
- *Question:*
  - *How to calibrate conclusions from one model relative to conclusions of another, if both model types can be used?*
  - *How to dissect the effect of various modeling assumptions at each level, in order to account for the side-effects of modeling in our conclusions?*

Roadmap

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  - *System dynamics; Markov chain; individual (patient) level spreadsheets; discrete event simulation*
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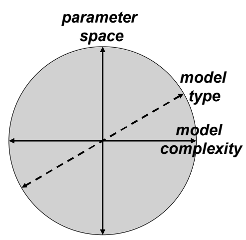
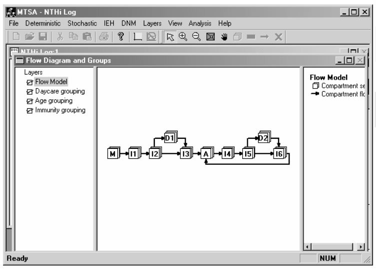
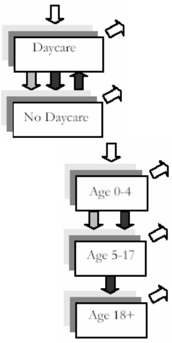
MTSA/ModelSeer with BioMedware

- GERMS: Implemented DEDS, validated with ODE separately
- MTSA: Assess effect of model on decisions regarding the analysis, surveillance, and control of infectious diseases.
- Sensitivity to changes in parameter values, model type, (e.g. ODE vs. MC vs patient-level) and model complexity (e.g. mixing, natural history)
- Progress:
  - Phase I: Prototype for NTHi mixing in patient setting done
  - Phase II: In progress



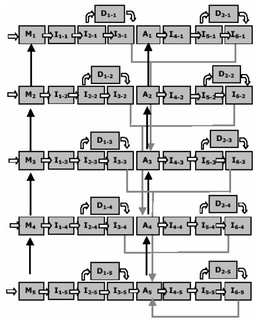
MTSA Prototype: NTHi model



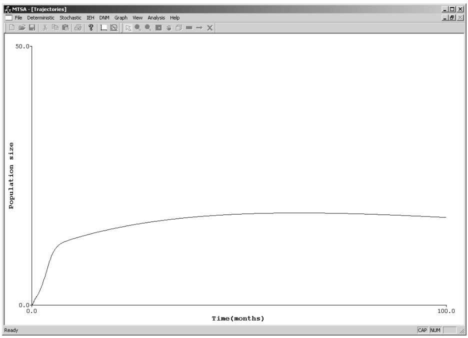


- *Individuals flow through ‘cross product’ of compartments, some combinations ‘illegal’*

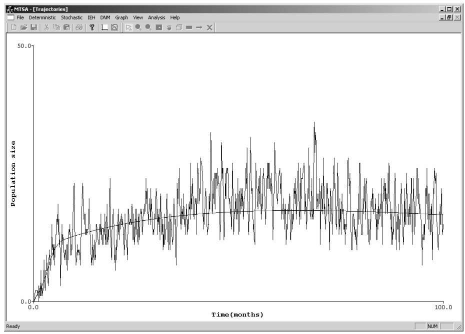
Example of cross-product



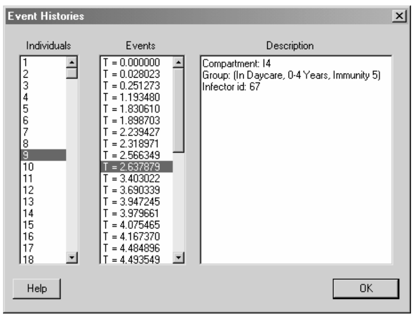
ODE Trajectory



Markov Chain Sample Path



Patient-Level Event History



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Untimed	*Decision tree*	*Stochastic decision tree*	*Stochastic decision tree with covariates*	

Summary: Model Type Sensitivity

- *Models that can be handed to different simulation engines may / may not give similar results (output or decision), but some differences are predictable*
  - *Large numbers*
  - *Discrete or continuous time*
- *Multiple types of models: useful for 'debugging'*
- *Some models might only be handed to one type of simulation engine*
- *People trained to model in system dynamics may approach problems differently than those trained in discrete-event simulation versus decision diagrams*
  - *Modeling is part of the understanding*
  - *Viva la difference!*

Conclusions

- **No models are right, some models are useful**
- **All model types make assumptions: Awareness**
- **Implied conclusions may depend upon model type**
- **Which model type to choose?**
  - **Basic question needs to trace individuals data ⇒ patient level (clinical trial, contact tracing, …)**
  - **Interactions (infection, constrained resources) ⇒ don't use 'untimed' model (e.g. decision tree)…**
  - **"Curse of dimensionality": Much patient/natural history heterogeneity ⇒ patient level simulation**
  - **Tightly constrained resources + waits affect health outcomes ⇒ patient level simulation**
  - **"Law of small numbers": Interactions + small numbers per compartment ⇒ stochastic models**
  - **Need to explore variability ⇒ stochastic model**
- **Simulation for visualization and communication**
- **Simulation runtimes and uncertainty analysis**

Professional Resources

- *Institute for Operations Research and Management Science (INFORMS)*
  - *Health Applications*
  - *Simulation (www.informs-cs.org)*
  - *"The Science of Better" www.informs.org*
- *Winter Simulation Conference*
  - *www.wintersim.org*

Related Works

- **Chick SE, Soorapanth S, Koopman JS, 2004, Microbial Risk Assessment for Drinking Water, In *Operations Research and Health Care: Handbook of Methods and Applications*, Brandeau, M.L., Sainfort, F., and W.P. Pierskalla,Eds., p. 467-494.**
- **Chick SE, Koopman JS, Soorapanth S, 2003, Inferring Infection Transmission Parameters That Influence Water Treatment Decisions, *Management Science*, 49(7): 920-935.**
- **Güneş, E.D., Chick, S.E., Akşin, O.Z., 2004, Breast Cancer Screening: Trade-offs in Planning and Service Provision, *Health Care Management Science*, 7(4): *in press***
- **Koopman JS, Chick SE, Riolo CP, Simon CP, Jacquez G, 2002, Stochastic effects on endemic infection levels of disseminating versus local contacts, *Mathematical Biosciences*, 180: 49-71.**
- **Koopman, J.S., Jacquez, G., Chick, S.E., 2001, New Data and Tools for Integrating Discrete and Continuous Population Modeling Strategies, In Population Health and Aging: Strengthening the Dialog between Epidemiology and Demography. M. Weinstein, A. Hermalin, M.A. Stoto Eds. *Annals of the New York Academy of Sciences*, 954: 268-294.**
- **Chick SE, Koopman JS, Soorapanth S, Brown ME, 2001, Infection Transmission System Models for Microbial Risk Assessment, *Science of the Total Environment*, 274(1-3): 197-207.**
- **Koopman, J.S., Chick, S.E., Riolo, C.S., Adams, A.L., Wilson, M.L., Becker, M.P., 2000, Modeling Contact Networks and Infection Transmission in Geographic and Social Space Using GERMS, *Sexually Transmitted Diseases*, 27(10): 617-626.**