Multiresolution Modeling & Evidence Generation:

Implications from Social Issues to Precision Health

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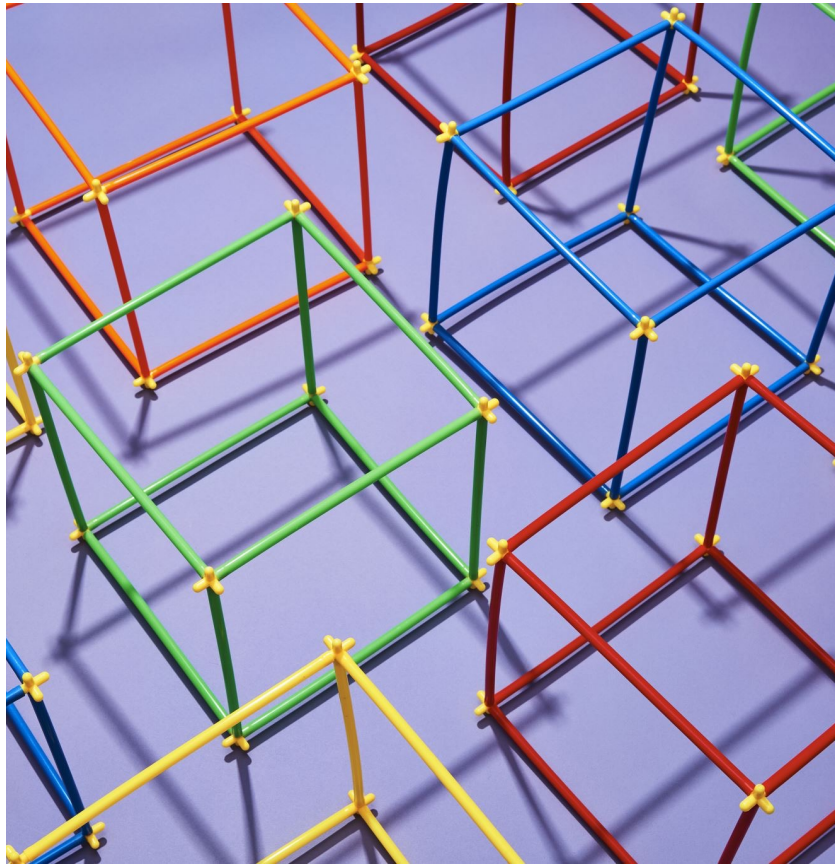
Outline

- Why care about modeling and evidence generation
  - Historical perspective
  - Modeling Challenges
- Quantitative Methods
  - Modeling techniques (lessons from COVID-19)
  - Evidence gaps and complexity linking to models
- Multiresolution Approach
- Conclusions



Health, Economics, and Social Choice

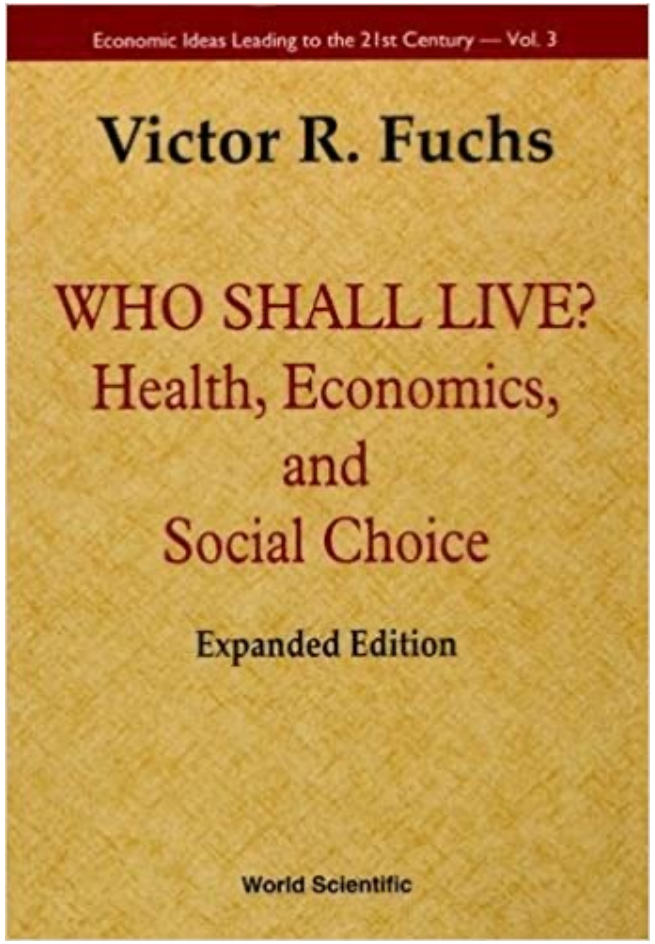
Fuchs 1974 book *Who Shall Live?*

Compared Nevada and Utah—which, despite their similar health care use patterns, experienced vastly different *life expectancy*.

- Now, the solution to the puzzle is well known
- *Health behaviors & social factors* are what really matter for longevity and quality of life.

The author stressed that result need to be replicated and reconsidered in light of

- *expanding data &*
- *statistical methods now available to researchers*

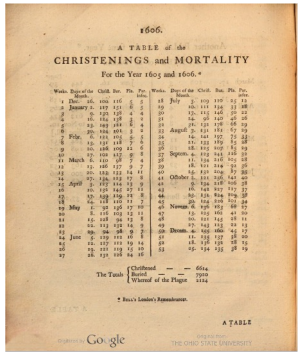


Why Big Tech fail in healthcare?

- Healthcare industry in the
  - US is a $4.00 trillion market
- Despite Big Tech companies, they've failed miserably
  - ***Google Health*** division disbanded
  - ***Apple's HealthHabit*** app scaled back
  - ***IBM's Watson AI and data analytics*** platform sold off
  - ***Amazon + JPMorgan Chase + Berkshire Hathaway's Haven Health*** disbanded
- Why?
  1. **Early success using only a small patients data sets**
  2. **Missing domain expertise: lack of complete understanding of the partnership model**
  3. **Unrealization that healthcare has "dirty data" problem (unstructured) and adaptive**

https://www.cio.com/article/189277/why-big-tech-cant-crack-healthcare.html?fbclid=IwAR3HMAEZ0CuwWCLt_HOes2itG_z8c_tdW5cJYtnh-soc78vDAjlZe-PxWh8

Primarily Last Two Decades of ID Modeling History



Before:

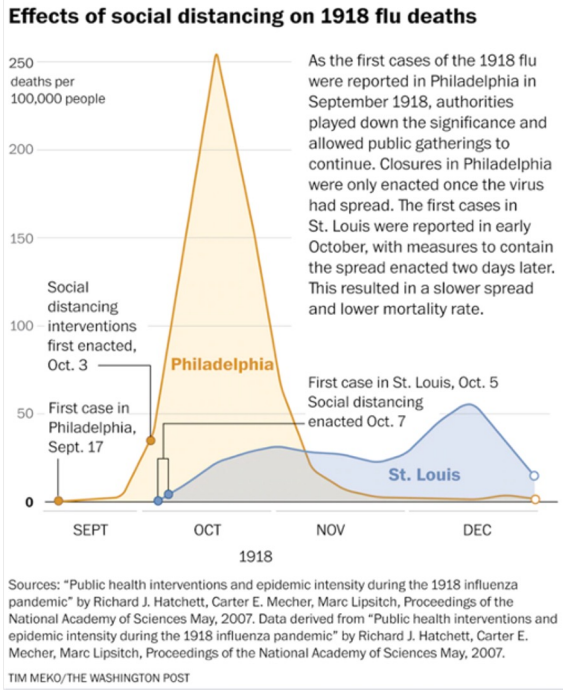
- *John Grant* (1620) – mortality data and stratified into disease category
- *Ronald Ross* (1902) - How effective does vector control need to be for Malaria? Models of malaria transmission were some of the first compartmental description and threshold behavior

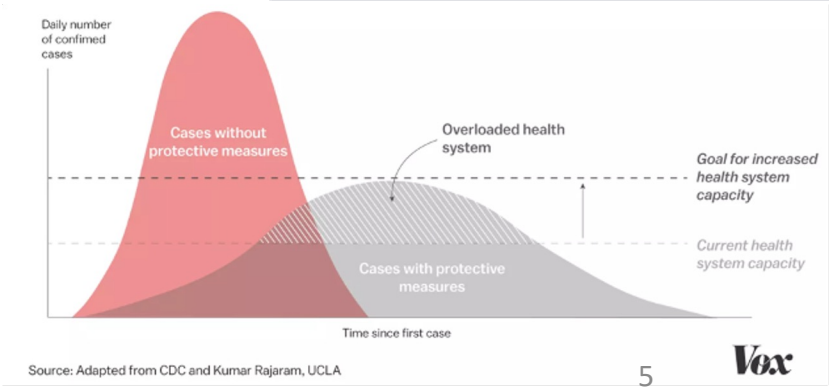
This Century:

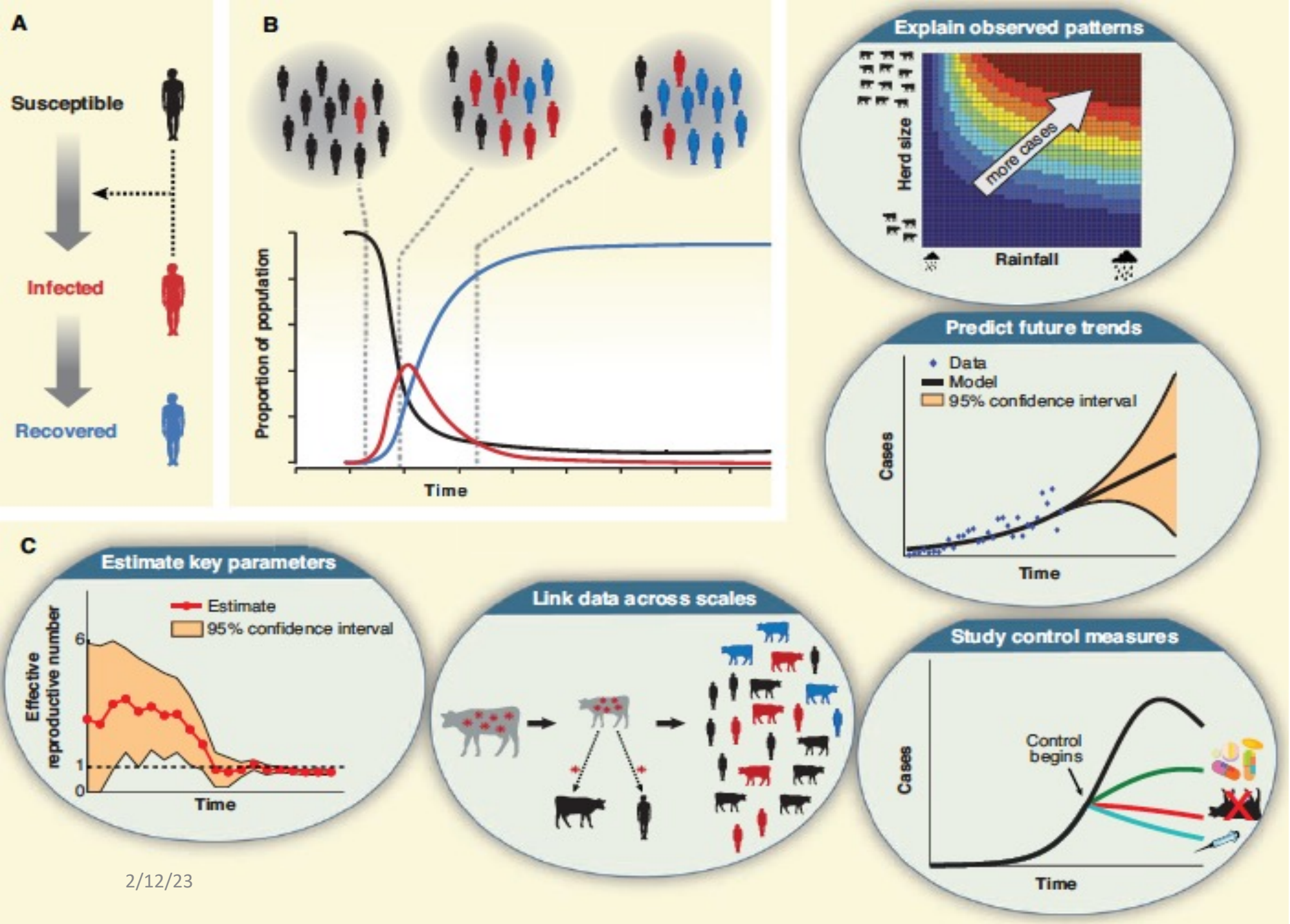
- *Foot and Mouth disease* – 2001-2003 How should the epidemic be controlled?
  - *The first example of the regular integration of emerging data into modelling efforts during an ongoing outbreak to inform decision making (to cull infected animals)*

- *911, Anthrax, SARS-CoV1, Influenza* (2002-2004)
  - Biosurvillence and Preparedness Task force was established in 2005 – flattening the curve
  - During 1918 Spanish Flu outbreak, No one knows what was killing them
  - In 2005, 1918–1919 pandemic virus was sequenced in its entirety

- *Flu forecasting* (2013-present)







How & what we can do with math models?

Lloyd-Smith, J. O., George, D., Pepin, K. M., Pitzer, V. E., Pulliam, J. R., Dobson, A. P., ... & Grenfell, B. T. (2009). Epidemic dynamics at the human-animal interface. *science*, *326*(5958), 1362-1367.

LIMITATIONS & EXTENSIONS OF CLASSICAL EPIDEMIC MODELS

Evolution of ***strains*** and spillover effects

Heterogenous/adaptive ***population behaviors*** (to disease, media, & other life-events) Infectiousness and wanning immunity

Interactions with other diseases (infectious and ***chronic disease***)

Impact of ***interventions on disease*** spread (e.g., vaccination nationalism)

Political inclination / will, public goods, and misinformation

Population heterogeneity / diversity and value for all stakeholders

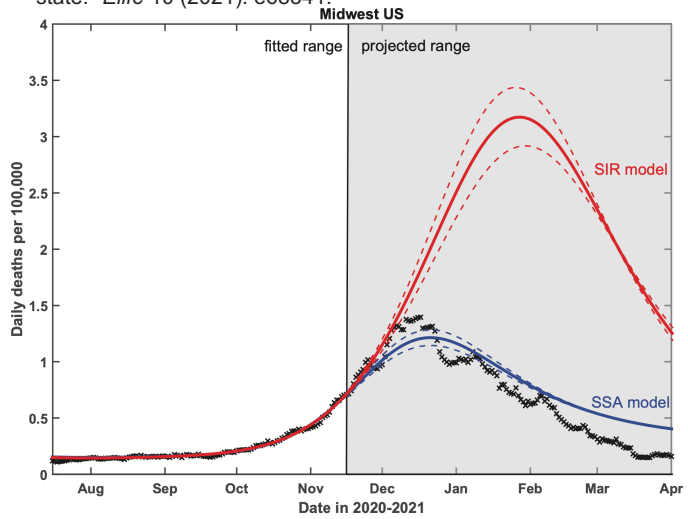
Modeling Techniques

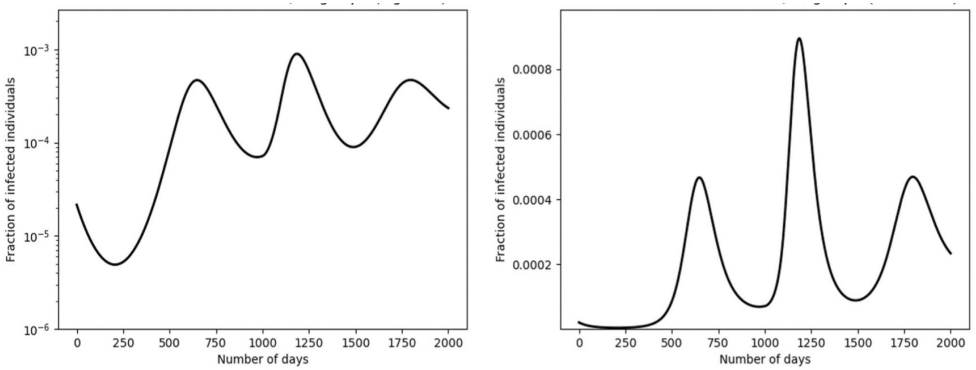
Capturing Disease Dynamics: Plateau, Rebounds & Oscillations

Population mixing patterns

Stochastic social activity (SSA) model: fitted up to November 17, 2020

Tkachenko, Alexei V., et al. "Stochastic social behavior coupled to COVID-19 dynamics leads to waves, plateaus, and an endemic state." *Elife* 10 (2021): e68341.





$$\frac{\partial S(t,a)}{\partial t} = d\frac{\partial^2 S(t,a)}{\partial a^2} - \beta(a)S(t,a)\frac{I(t)}{N}$$

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{I(t)}{N}\int_0^1 \beta(a)S(t,a)\,da - \gamma I(t),$$

Multiple epidemic rebounds

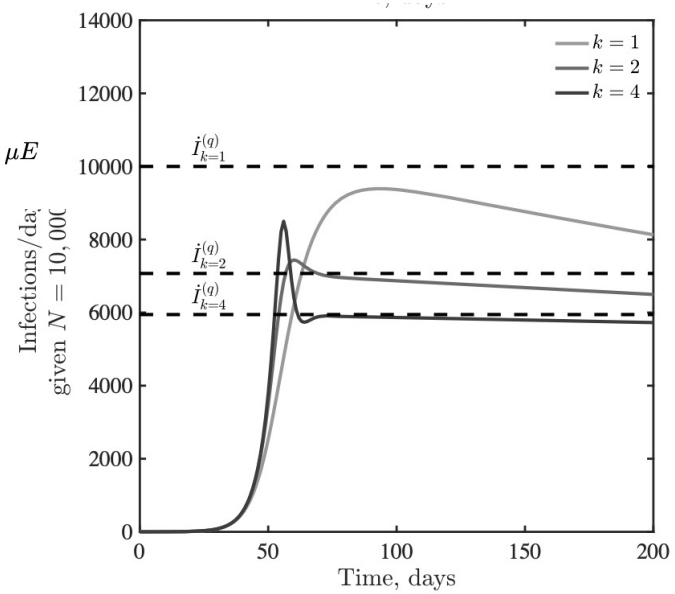
Berestycki, Henri, et al. "Plateaus, rebounds and the effects of individual behaviours in epidemics." *Scientific reports* 11.1 (2021): 1-12.

$$\dot{S} = -\frac{\beta SI}{\left[1+(\delta/\delta_c)^k\right]}$$

$$\dot{E} = \frac{\beta SI}{\left[1+(\delta/\delta_c)^k\right]} - \mu E$$

$$\delta = \dot{D}$$

Plateau- or shoulder-like phenomena

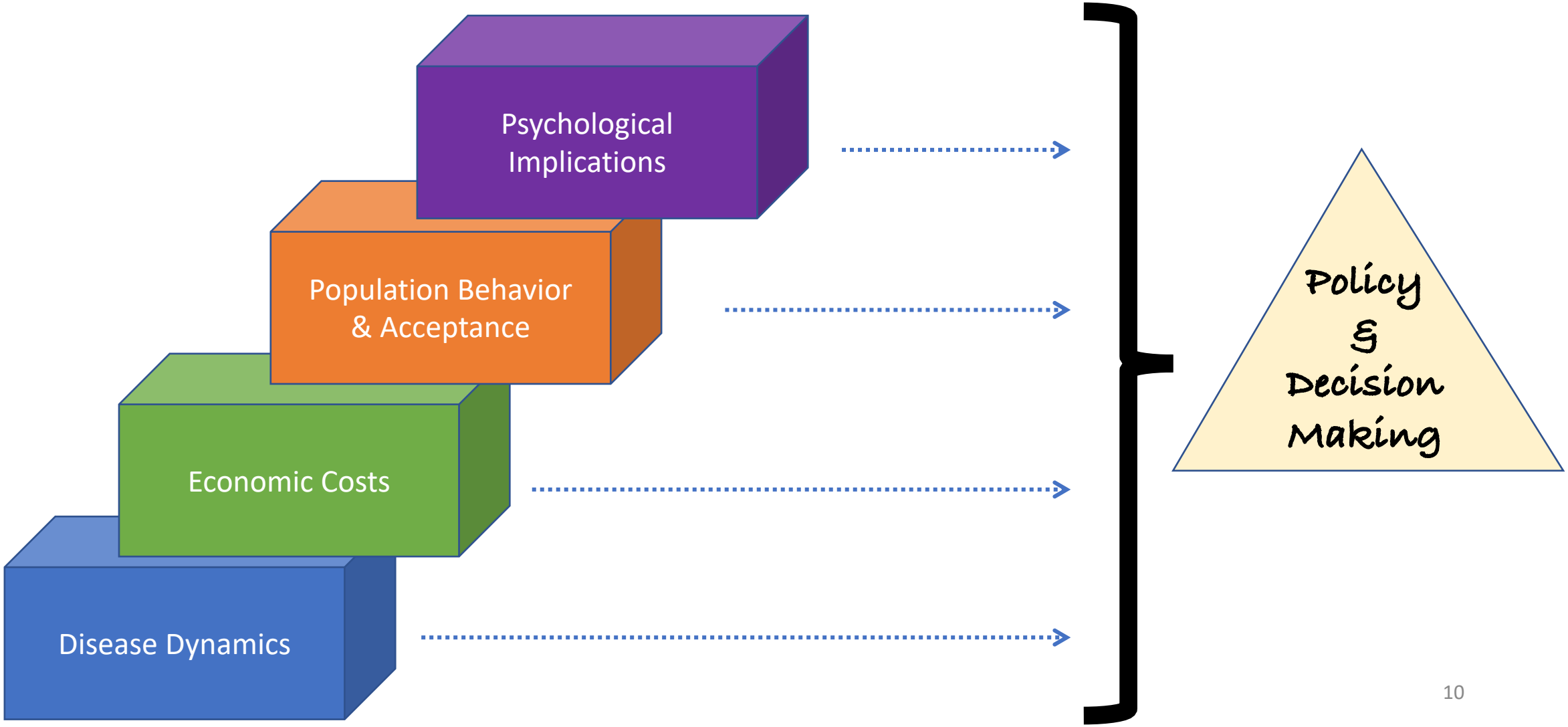


Population behaviors due to interventions

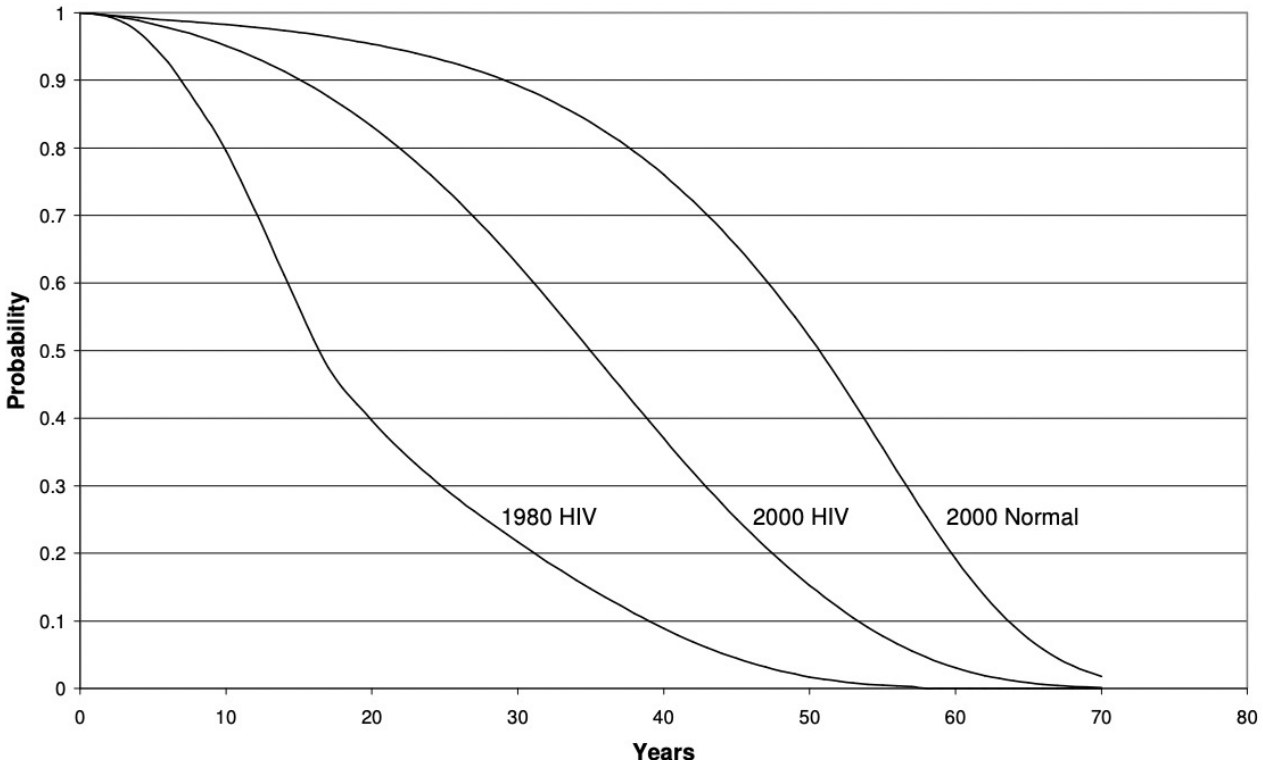
Fear of infection

Weitz, Joshua S., et al. "Moving Beyond a Peak Mentality: Plateaus, Shoulders, Oscillations and Other 'Anomalous' Behavior-Driven Shapes in COVID-19 Outbreaks." *medRxiv* (2020).

Modeling values creation at various scale for policy and decision making



Value creation of HAART and HIV/AIDS Survival over time

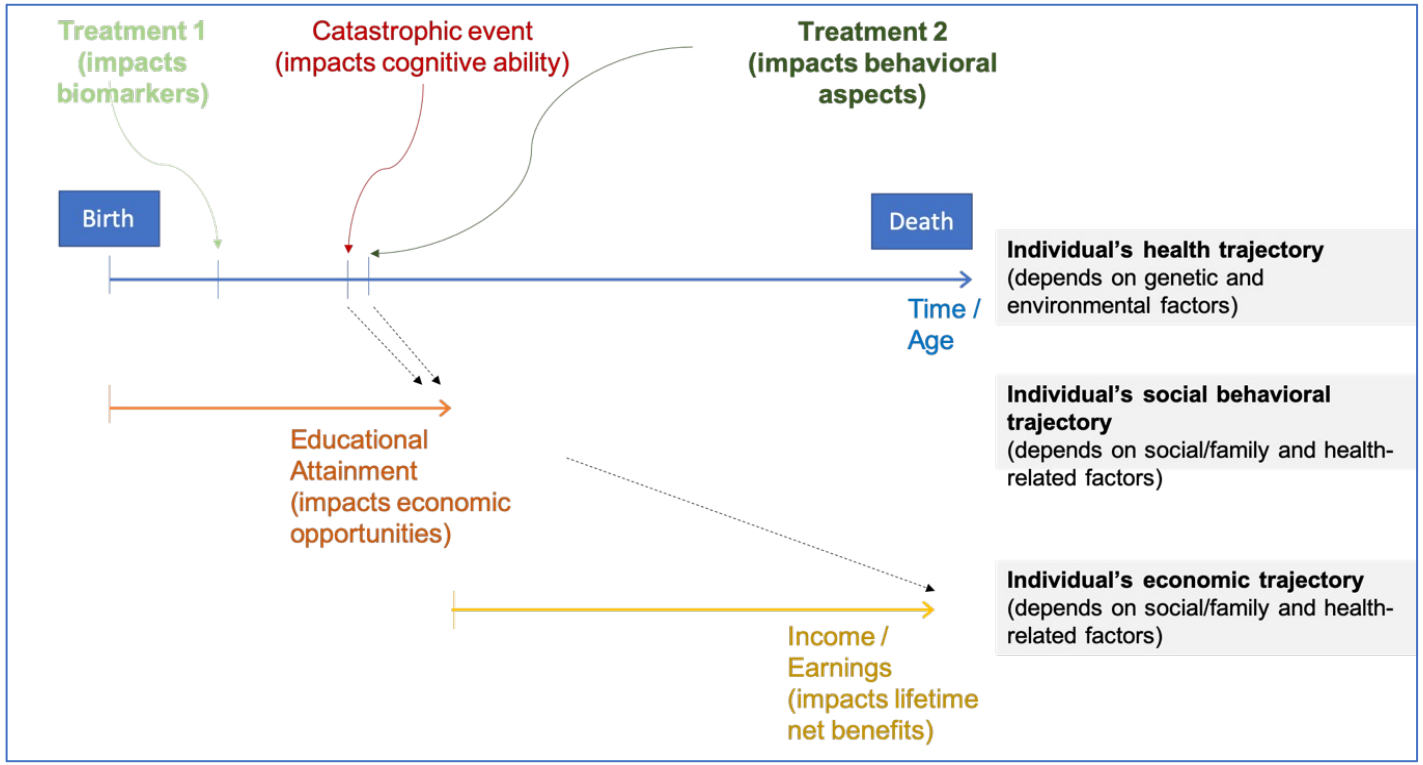


Philipson, Tomas J., and Anupam B. Jena. *Forum for Health Economics & Policy*. Vol. 9. No. 2. De Gruyter, 2006.

- Mid 1990s
  - Highly active antiretroviral therapy (HAART) but was expensive
- Life expectancy of HIV+AIDS (primarily due to HAART)
  - 22 years in 1984
  - 51 years in 2000
- Magic Johnson, a famous basketball player
  - In 1991, announced that he contracted HIV

5% of the <u>value creation</u> only went to innovators; most benefits to patients

Value of Treatment and Educational Attainment on Lifetime Income for SCD patient



Objective: How potential improvements in cognitive function generated in childhood through treatment for SCD influence lifetime income?

Method (System Science)

1. PKPD model
   - Linking treatment with biomarkers
2. Catastrophic model
   - Linking Hb level to risk of stroke
   - Linking stroke to IQ level
3. Regression models
   - linking cognitive function/IQ to educational attainment
4. Dynamic economic model
   - Linking academic achievement to life-time income/earnings

Model Results: In simulated SCD cohort

	Treated Group	Untreated Group
Experienced significant stroke	4.8%	7.9%
Average IQ	91.1	82.9
High school completed	76.1%	44.3%
Cumulative lifetime income	$x+$166,012	$x

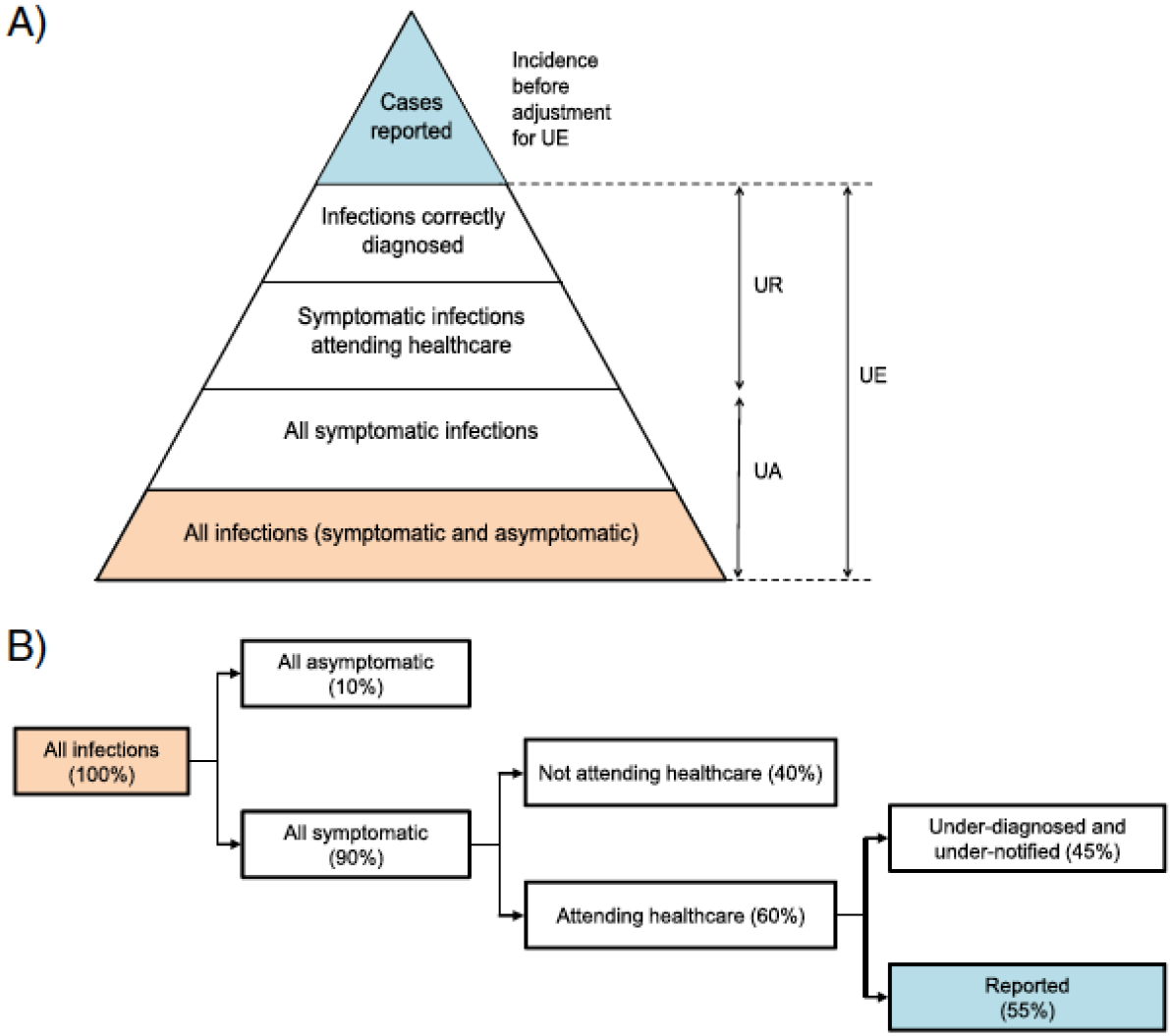
Evidence Gaps and Linking to Models

Definitions of Missing Information

Community level since not all cases seek healthcare (under-ascertainment; **UA**)

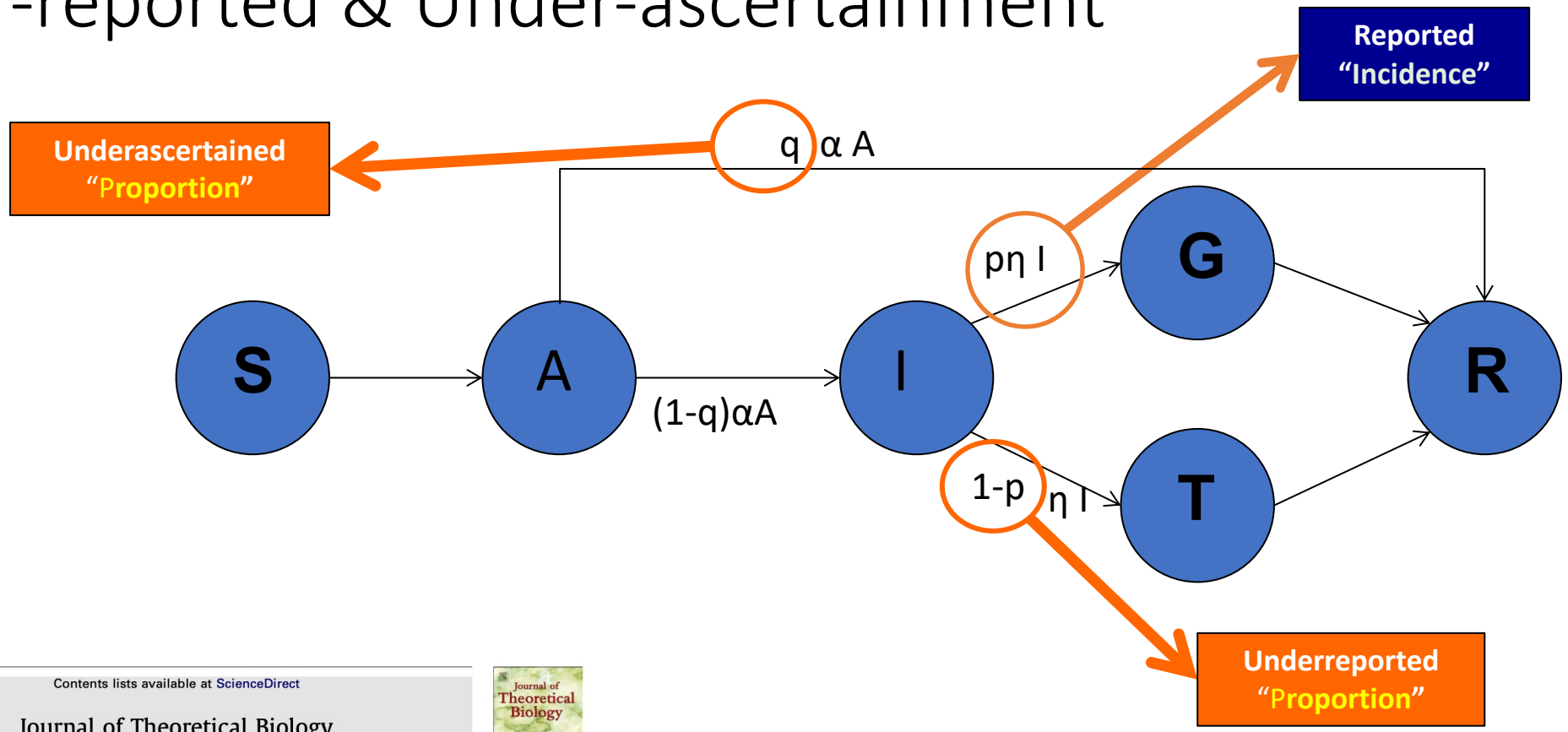
Healthcare-level, representing a failure to adequately report symptomatic cases that have sought medical advice (underreporting; **UR**)

Ways in which surveillance systems fail or are unable to reflect all infections (Underestimation; **UE**)



Gibbons, C.L., Mangen, M.J.J., Plass, D., Havelaar, A.H., Brooke, R.J., Kramarz, P., Peterson, K.L., Stuurman, A.L., Cassini, A., Fèvre, E.M. and Kretzschmar, M.E., 2014. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. *BMC public health*, *14*(1), p.147.

Under-reported & Under-ascertainment



Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Transmission dynamics and underreporting of Kala-azar in the Indian state of Bihar

Anuj Mubayi [a,b,d,f,*], Carlos Castillo-Chavez [a,b,c,e], Gerardo Chowell [a,b], Christopher Kribs-Zaleta [d], Niyamat Ali Siddiqui [g], Narendra Kumar [g], Pradeep Das [g]

G → Patients that are correctly diagnosed and treated in healthcare facilities

T → Patients not accessing reporting agencies or are incorrectly getting diagnosed

A → Asymptomatic which may self-recover

I → Clinical symptomatic cases

Bihar's overall underreporting declined by about 17% from 2003 (88%) to 2005 (73%).

Malaria Model

Parameter	Method	Data
A, d, alpha	• Directly • Submodel • Reduction	Demographic data from census & literature
theta, theta0, L	• Indirectly • Submodel • Scaling	Mosquito abundance time series & LSQ method
theta1, gamma, gamma1, K	• Indirectly • Submodel • Scaling	Bacteria (under control) time series & PCS method
beta, lambda	• Indirectly • Full model	Case incidence time series &LSQ method

$$\frac{dY}{dt} = \beta(N-Y)M_I - (\nu+\alpha+d)Y$$
$$\frac{dN}{dt} = A - dN - \alpha Y$$
$$\frac{dM_I}{dt} = \lambda(M-M_I)Y - (\theta_0+\theta_1 B)M_I$$
$$\frac{dM}{dt} = \theta M\left(1-\frac{M}{L}\right) - (\theta_0+\theta_1 B)M$$
$$\frac{dB}{dt} = \gamma B\left(1-\frac{B}{K}\right) + \gamma_1 MB.$$

Humans

Mosquitoes

Bacteria

Total → 9 parameters

Reduction

A

Parameters **directly** obtained from literature and are fixed **(A, d, alpha; 3 parameters)** Census/demographic/epidemiol gocial data

Scaling

Parameters indirectly estimated from entomological data and **submodel** ***(7 parameters)***

$$\frac{dM_h}{dt} = M_h\left(\theta(1-30\frac{M_h}{L}) - (\theta_0+\theta_1 B)\right)$$
$$\frac{dB}{dt} = B\left(\gamma(1-\frac{B}{K}) + 30\gamma_1 M_h\right)$$

where $M_h = M/30$

D

Parameters **indirectly** estimated from incidence time series data and **full model** and curve fitting method (least square) ***(2 parameters)***

$$\frac{dM_h}{dt} = M_h\left(\theta(1-30\frac{M_h}{L}) - (\theta_0 \cdots\right.$$

If B=0, estimate ϑ, ϑ_0 and L using time series mosquito abundance timeseries data and curve fitting method (weighted least square)

B

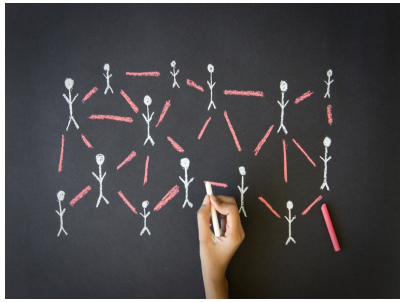
$$\frac{dM_h}{dt} = M_h\left(\theta(1-30\frac{M_h}{L}) - (\theta_0+\theta_1 B)\right)$$
$$\frac{dB}{dt} = B\left(\gamma(1-\frac{B}{K}) + 30\gamma_1 M_h\right)$$

If B /=0, estimate γ, ϑ_1, γ_1 , *K*. using control bacterialllll ...data and curve fitting method (Pearson chi-square). Also, using time series of density of bacteria and mosquito abundance

C

Multiresolution Approach

Lesson Learned or Unlearned



Lesson Learned:

- Sensitive to input parameters
  - Resulted in huge variations in results
- We placed much emphasis on prediction
  - rather than understanding how outbreak is spread

Unlearn and understand "What can we do with models":

- Pairwise comparisons of intervention strategies are better
- Open-source models/codes
- Ensure that we do not make too much overly confident prediction
  - when data is scare or unreliable
- Model should evolve in line with changing human behaviors and culture
  - such as the strength of distancing protocols, wearing of masks, or propensity to follow government advice

UoW IHME Model

Method:

- Statistical machine learning methods
- Mortality prediction using extrapolation of all the available data

Issues:

- Does NOT include dynamics of actual spread of disease
- They have huge confidence interval in their prediction

Imperial College Model

Method:

- Computational Model is a multi-agent model
- Estimate interactions using *census data* and making guesses on contacts using *public transportation* and with certain stochasticity
- Estimate disease dynamics at an individual level and simulate efficacy of various interventions

Issues:

- Very complex and huge number of parameters (simple model can do the job) …15000 lines of code… [earlier not available]
- Mortality rate predictions can be quite variable depending on the age and comorbidities of those contracting the virus

Bulletin of Mathematical Biology (2022) 84:3
https://doi.org/10.1007/s11538-021-00959-4

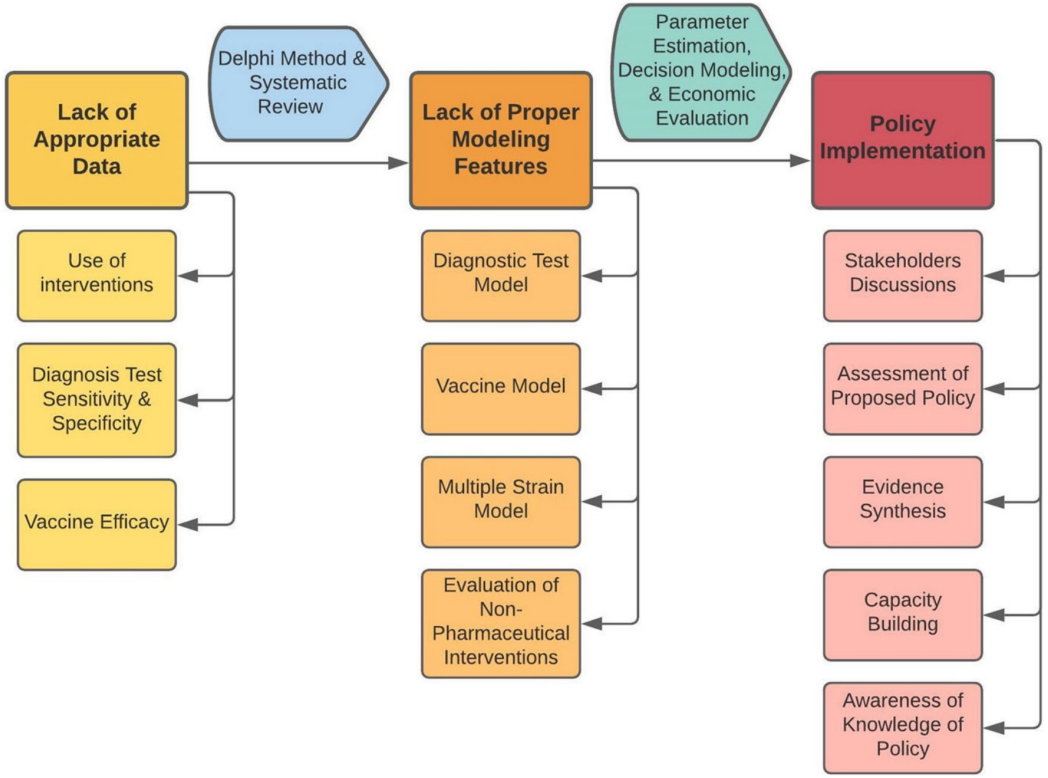
Society for Mathematical Biology

PERSPECTIVES

The Hard Lessons and Shifting Modeling Trends of COVID-19 Dynamics: Multiresolution Modeling Approach

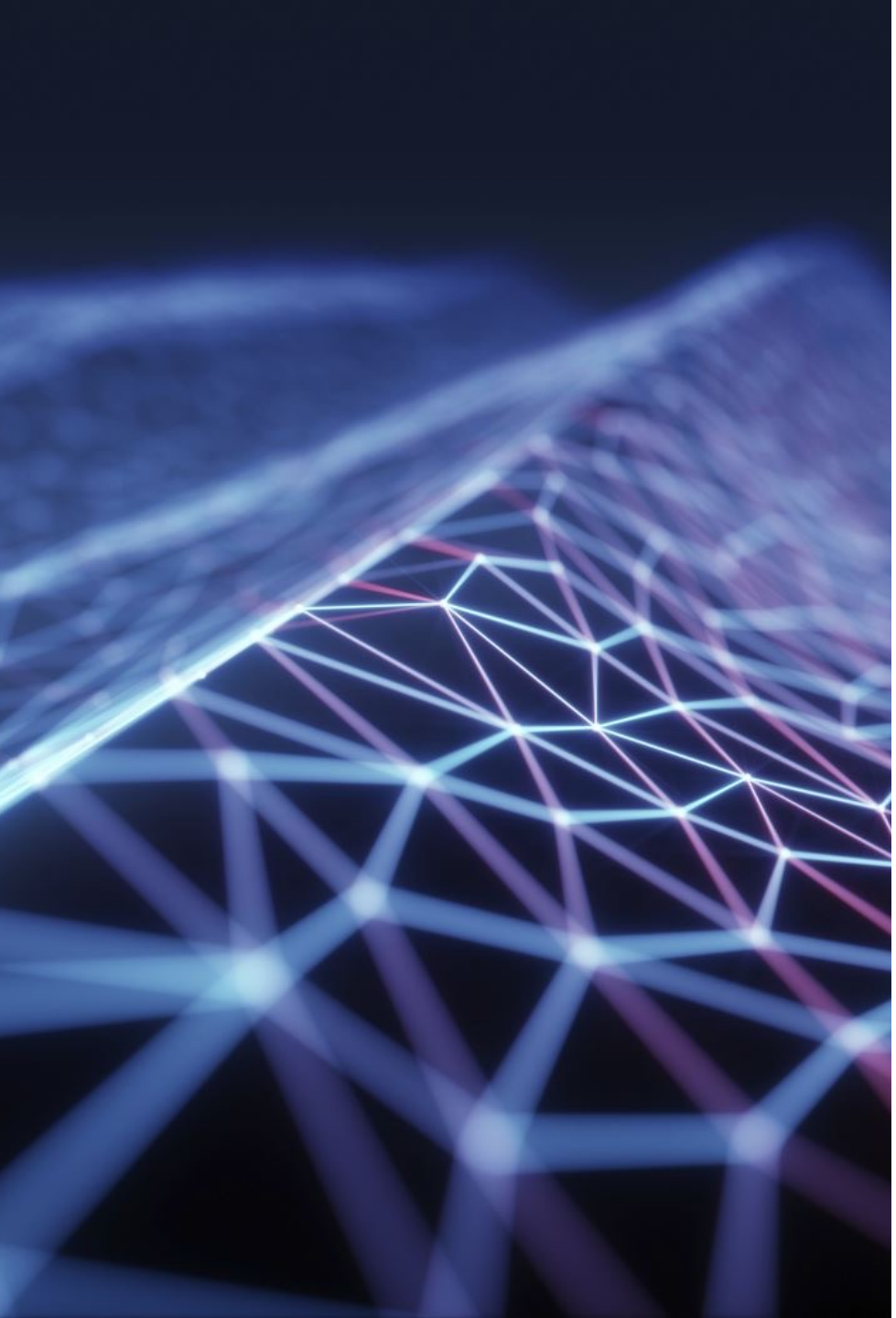
Olcay Akman[1,2] · Sudipa Chauhan[3] · Aditi Ghosh[1,4] · Sara Liesman[1,2] · Edwin Michael[5] · Anuj Mubayi[1,2,6,9,10] · Rebecca Perlin[1] · Padmanabhan Seshaiyer[7] · Jai Prakash Tripathi[8]

Received: 6 April 2021 / Accepted: 12 October 2021



Multiresolution Modeling Approach

1. Epidemic Nowcasting
   - Changing reporting methodology,
   - Newly available biological information,
   - Reasons for delays
2. Multi-objective Optimization Problem
   - Ensemble of models
   - Cost-benefit analysis
   - For multiple stakeholders
3. Participatory Modeling
   - Community partnerships
   - Feedback mechanisms through cycle of modeling



Conclusions

COVID highlighted challenges associated with measuring value

- Partnership model is key for value estimates
- Added value via choice of modeling technique -
  - Not married to type of model or dataset
  - Use of simple but data-driven practical framework

Whether the objective of a model is inference, forecasting, or intuition-building

- The handling of uncertainty should be a central concern for value creation

Emerging technology and pandemic-related disruptions are redefining the skills people need to succeed in their jobs.

- Building community of new generation of scientists
- Science communication

Thank you

ISPOR Value Flower
(Lakdawalla et al., 2018)