On Complex Systems Theory and Population Health: Should the Twain Meet?

- **background – Ann Arbor; analytical needs**
- **what is meant by *complex systems theory, population health, models***
- **challenge: new generation of models, to address important and practical questions**
- **approaches: "meta-synthesis", and bridging toy / theoretical ↔ industrial strength models**

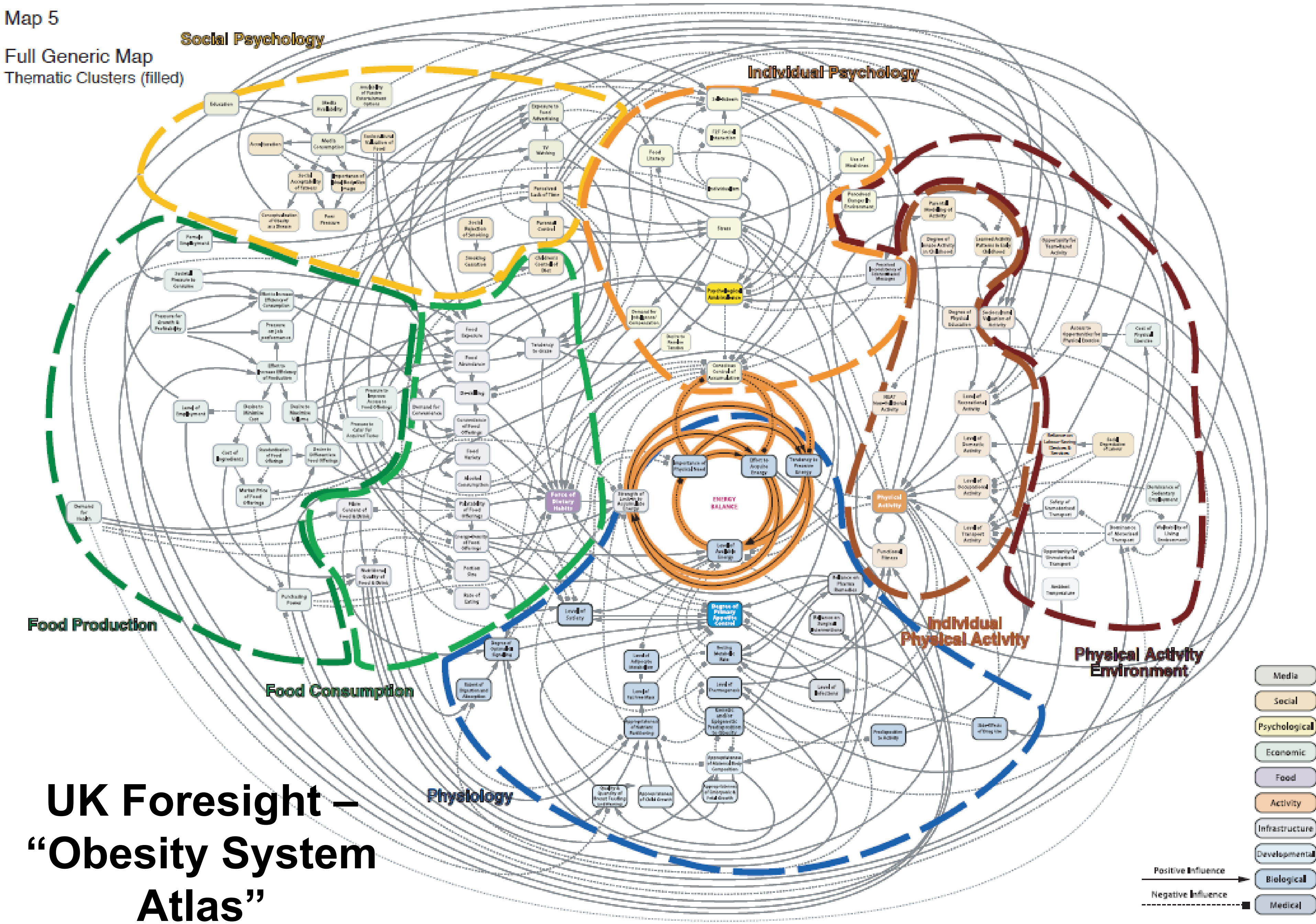
Michael Wolfson, Statistics Canada

What Do We Mean by *Population Health*?

- **"…layered multilevel understandings, a multiplicity of pathways, and possibilities for reciprocal influences."** (Kaplan on "Social Epidemiology", 2004)
- **"A group of individuals behaves as a population system when patterns of connections among individuals influence population health outcomes."** (Koopman and Lynch, AJPH, 1999)
- **"…at what stages of the life course, and in what settings, can we most effectively intervene to reduce the major burdens of disease, bearing fully in mind the complex causal webs involved…"** (conversation with John Frank, 2007)

Map 5

Full Generic Map
Thematic Clusters (filled)

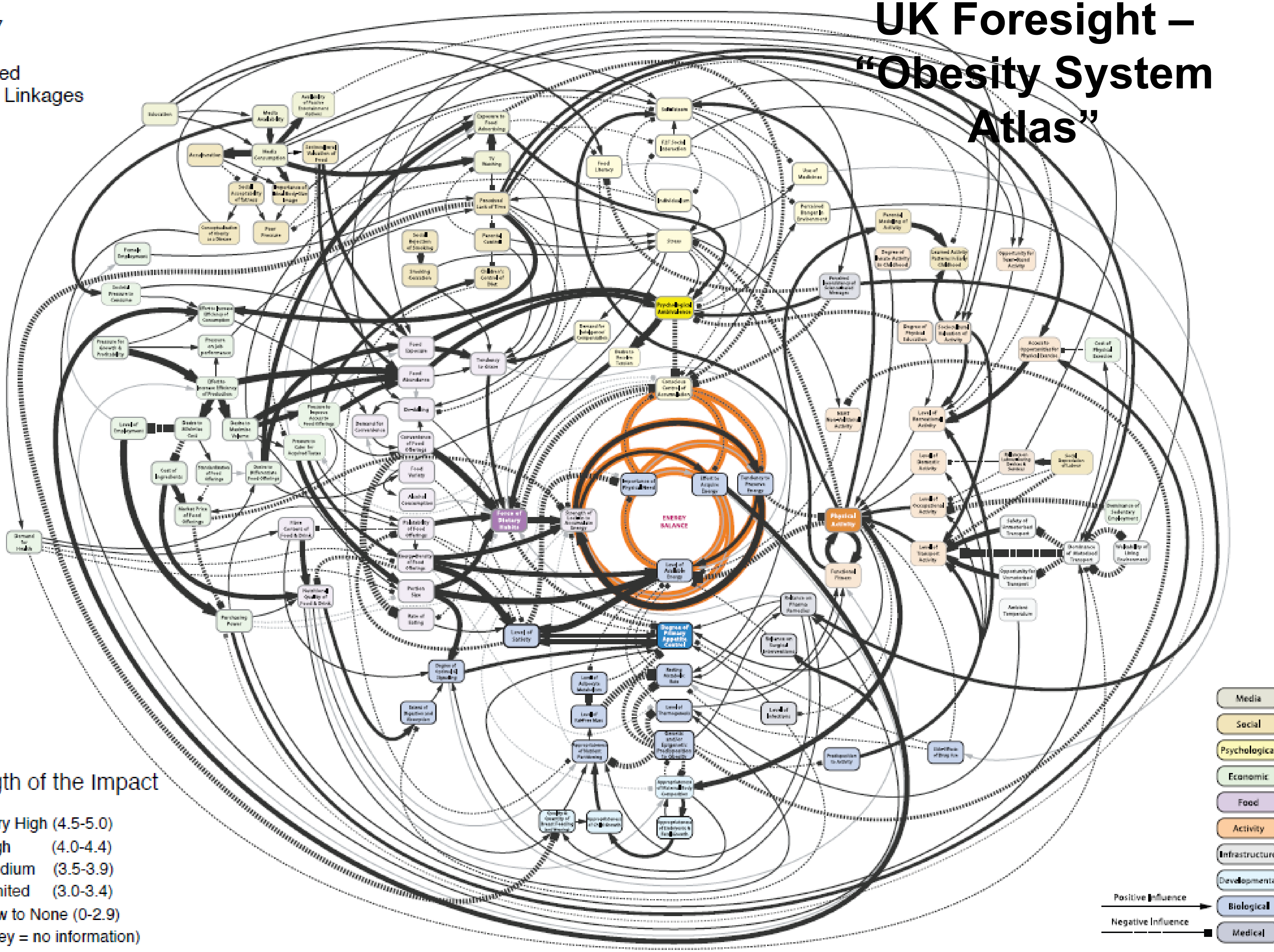


UK Foresight – "Obesity System Atlas"

Map 27

Weighted Causal Linkages

UK Foresight – "Obesity System Atlas"



Strength of the Impact

- Very High (4.5-5.0)
- High (4.0-4.4)
- Medium (3.5-3.9)
- Limited (3.0-3.4)
- Low to None (0-2.9)
- (grey = no information)

Caveat re Theories of Population Health

Multiple causation is the canon of contemporary epidemiology, and its metaphor and model is the 'web of causation'. … (But) relatively little work has been devoted to developing the concepts and framework of what might be called epidemiologic theory… (and) even less (to) the fundamental question posed by the web's suggestive imagery: who or what is the 'spider' responsible for its array of factors?

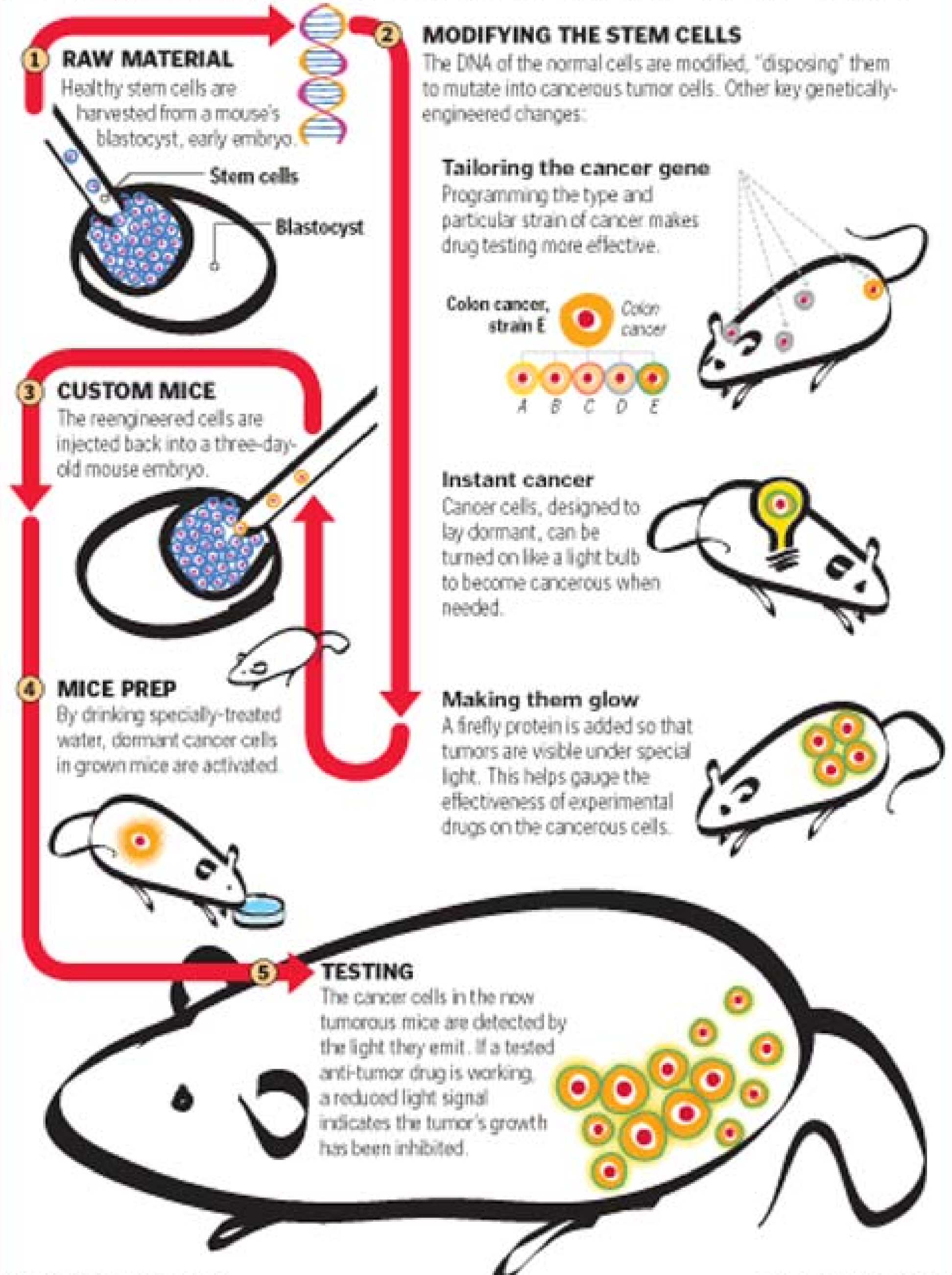
(Nancy Krieger, Soc Sci & Med, 1994)

What Do We Mean by *Model* ?

- huge variety of meanings!

Building a better lab mouse

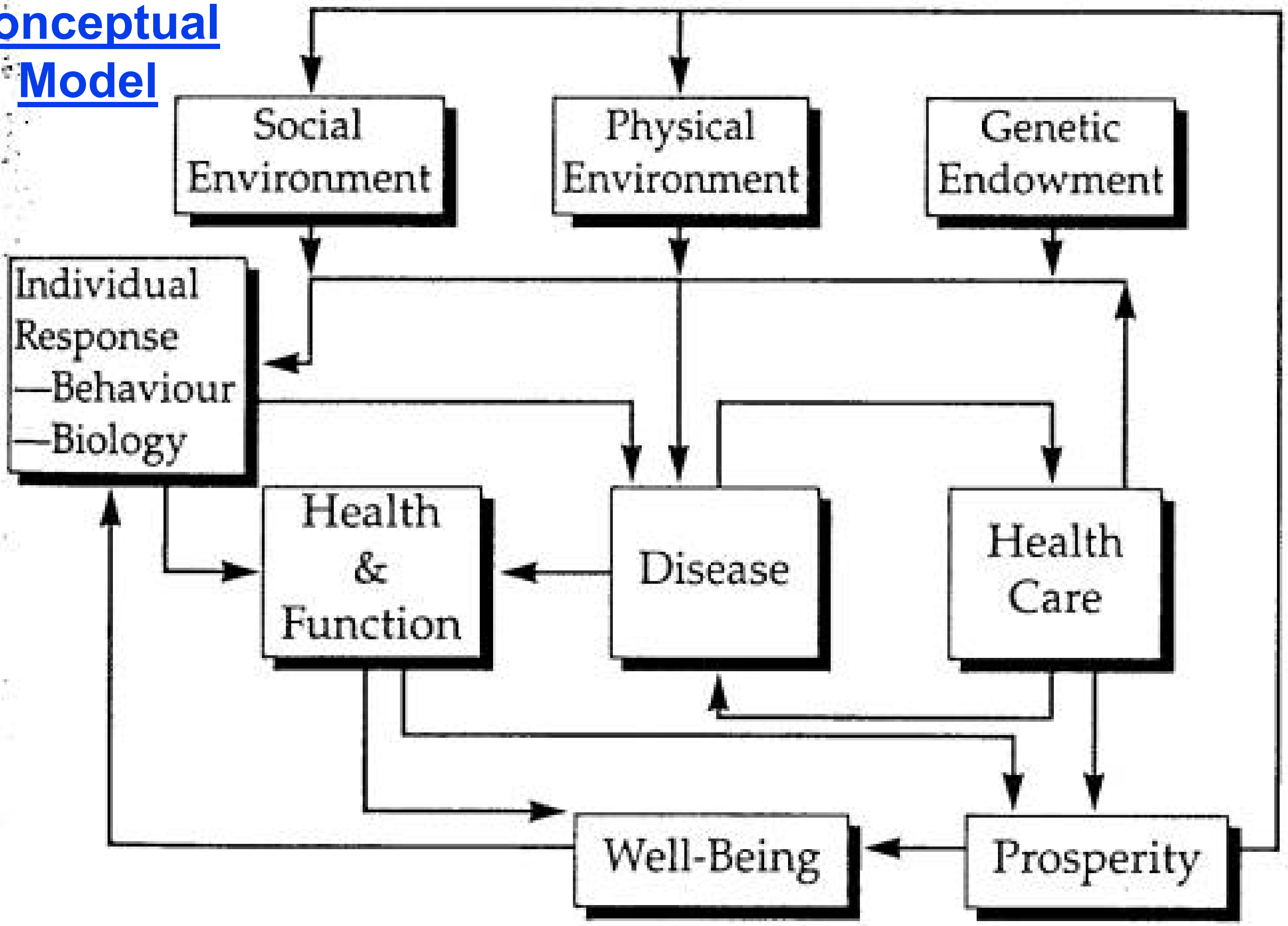
Through genetic engineering, AVEO Pharmaceuticals Inc. has created a lab mouse that can better predict the effectiveness of experimental anti-cancer drugs. The engineered mouse:



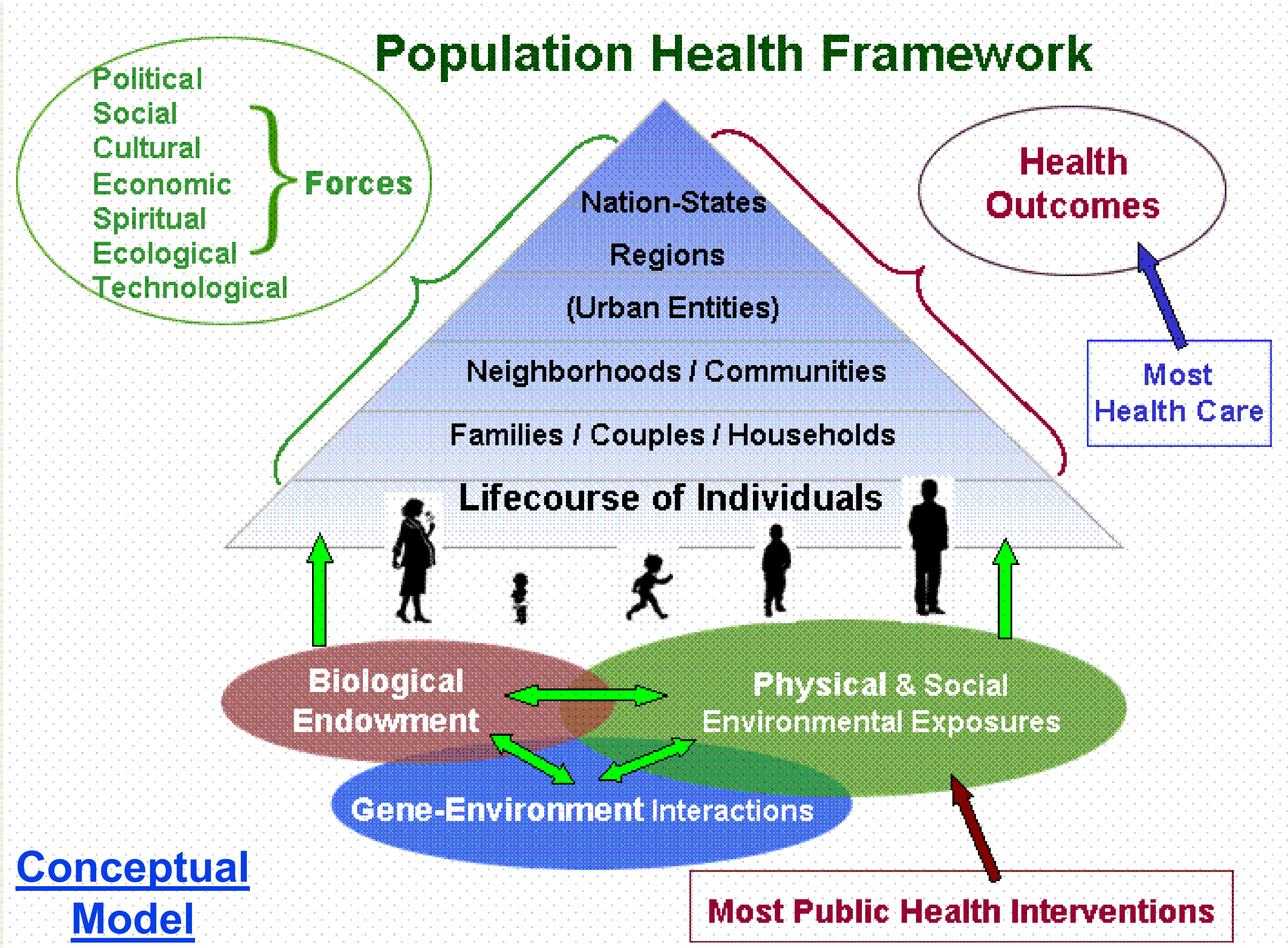
SOURCE: AVEO Pharmaceuticals, Inc.

JAMES ABUNDIS/GLOBE STAFF

Conceptual Model



Evans and Stoddart, 1999



Population Health Framework
Political
Social
Cultural
Economic
Spiritual
Ecological
Technological
Forces
Health Outcomes
Nation-States
Regions
(Urban Entities)
Neighborhoods / Communities
Families / Couples / Households
Lifecourse of Individuals
Most Health Care
Biological Endowment
Physical & Social Environmental Exposures
Gene-Environment Interactions
Conceptual Model
Most Public Health Interventions

Re Conceptual Models

- all seek to highlight causal pathways
- “everything affects everything else”
- general consensus on
  - multi-level
  - life course
  - dynamics
- but major challenges with empirical grounding
  - constructs ↔ measurable variables
  - causal webs ↔ operational / quantified / algorithmic relationships among variables

What Do We Mean by *Complex…Systems Model* ?

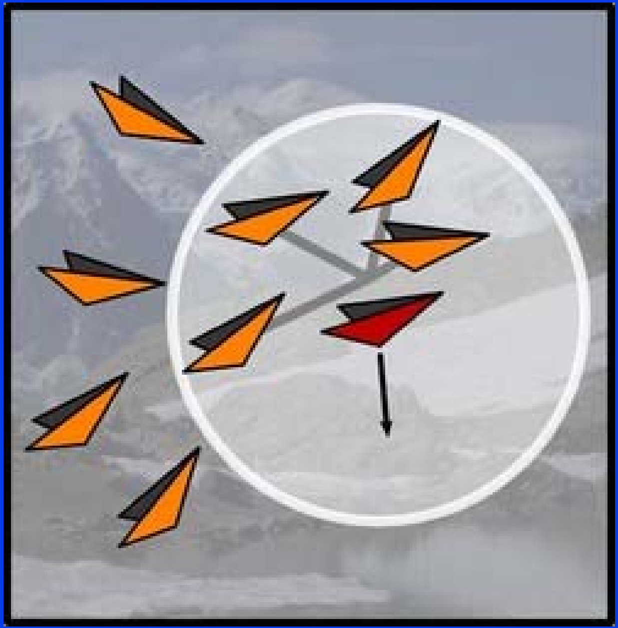
- realized as computer software (within many programming environments)
- this software typically *simulates* the co-evolution of an arbitrarily large set of *agents*
- each agent is endowed with *laws of motion*, often defined in terms of a *repertoire of behaviours* – a set of algorithms describing what the agent does under varying *circumstances*
- in turn these *circumstances* are a combination of
  - internal states, including their histories
  - states of other ("nearby" or "linked") agents
  - and a more or less fully specified "environment" within which the agents evolve and interact

"Emergence" Models

- the "holy grail" of complex adaptive (typically agent-based) systems models
- simplistically: emergence is when the whole is greater than the sum of its parts
- emergence refers to the way complexity, and (more fun) life-like patterns arise out of a number of relatively simple interactions
- clearly links to population health in so far as
  - "determinants of health" for an individual include social factors that inhere in characteristics of the population,
  - and these are not simple aggregates of individual characteristics

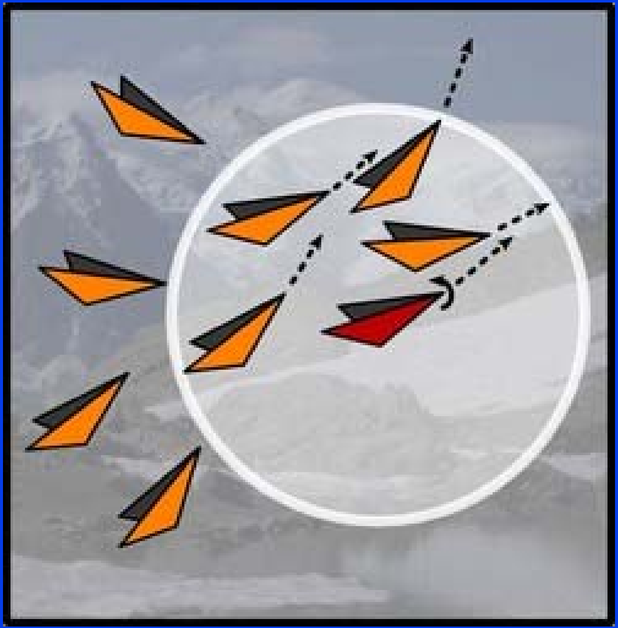
Parker's (1986) Boids

Separation



Steer to avoid crowding with local flock mates.

Alignment



Steer toward the average heading of local flock mates

Cohesion

Steer to move toward the average position of local flock mates

Digression – Neoclassical Economics Models, *NOT*

- "Now my children, let us assume…" (typical opening line, Frank Hahn, 1970s graduate seminar)
- "Individuals consume n goods X_i, i = 1, 2, … , n and a numeraire Y. There are H individuals whose preferences are characterized by a linearly separable utility function, $U = u_h(x_h; \alpha) + y_h$, h = 1, 2, …H where $x_h = (x_{h1}, x_{h2}, \dots, x_{hn})$; x_{hi} is the quantity of good i and y_h is the quantity of the numeraire consumed by individual h. The utility function u_h is assumed to be strictly concave and differentiable in x_h. Linear separability is assumed to eliminate distributional considerations…" (Sheshinski, 2007)

"Rite of Passage" / Mainstream Economics Model

- "The young Econ, or "grad," is not admitted to adulthood until he has made a "modl" exhibiting a degree of workmanship acceptable to the elders of the "dept" in which he serves his apprenticeship. …The Math-Econ are in many ways the most fascinating, and certainly the most colorful, of Econ castes. … show(ing) many cultural patterns that we are wont to associate with religious orders or sects … (They) make exquisite modls finely carved from bones of walras. If some of these are "useful"… it is clear that this is purely coincidental in the motivation for their manufacture."

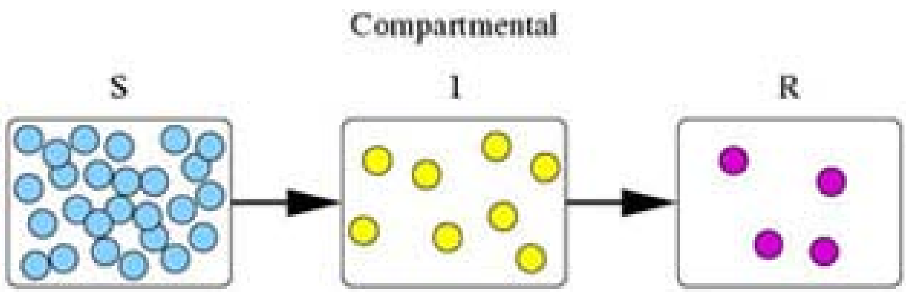
"Life Among the Econ" Axel Leijonhufvud

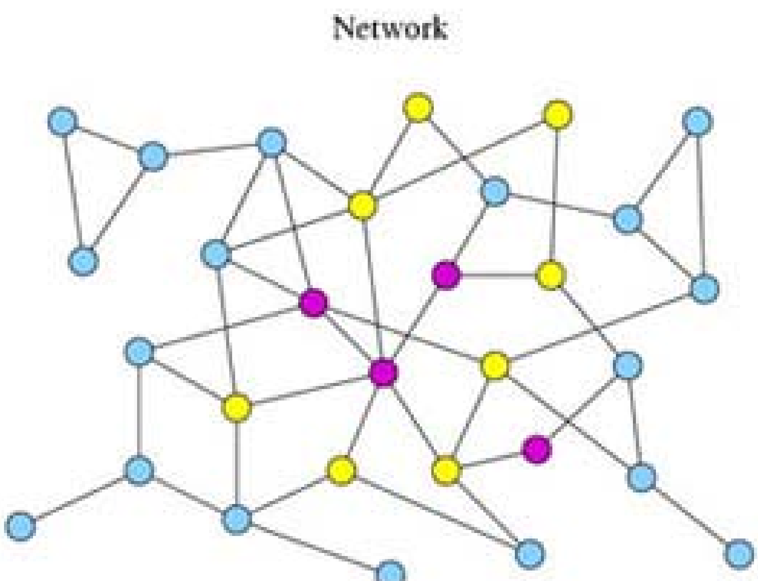
Standard Infectious Disease Compartment (ODE) Models and Random Mixing…vs Network Models

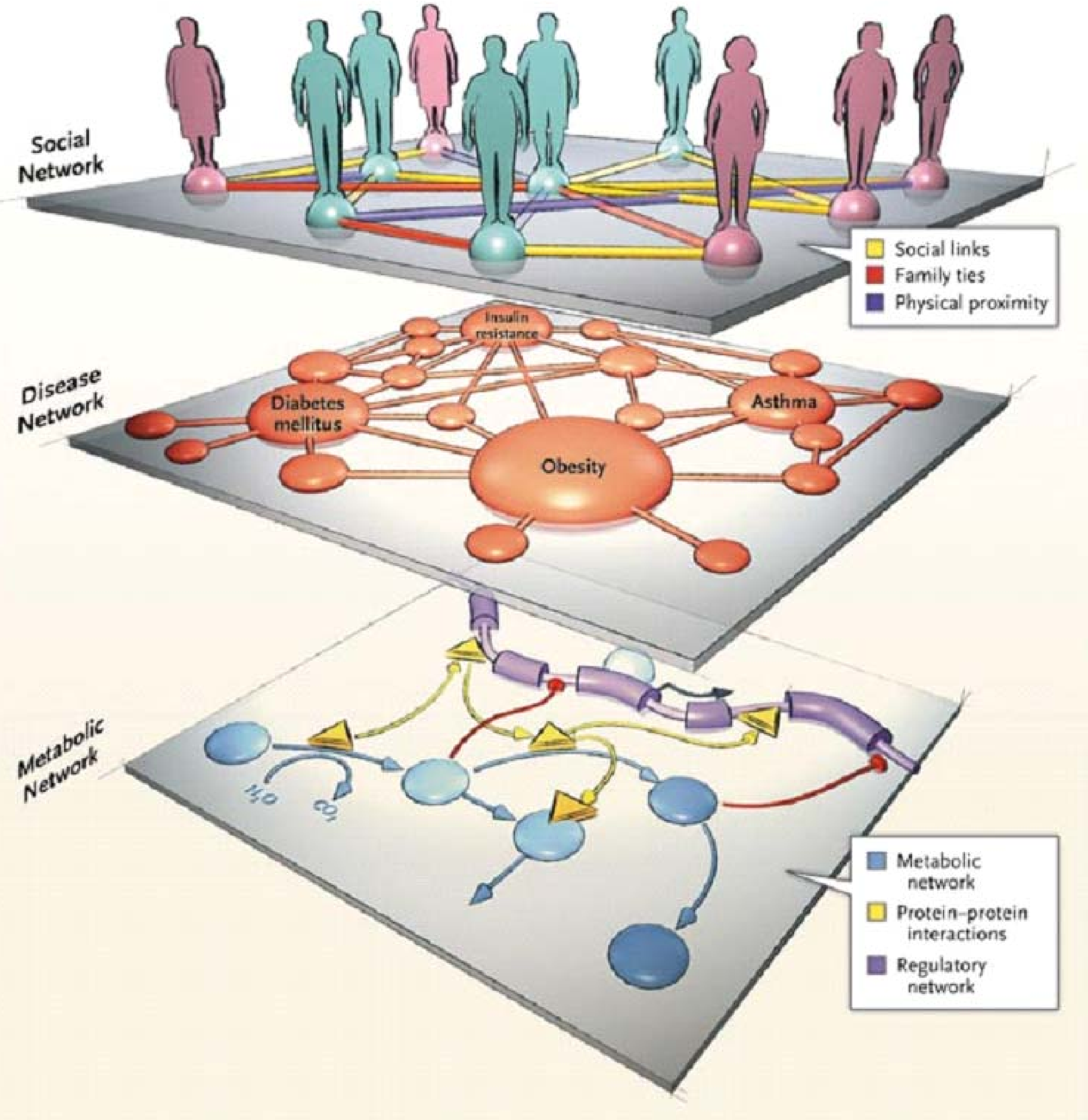
Susceptible (S), $$\dot{S} = -rIS$$

Infected (I), and $$\dot{I} = rIS - aI$$

Removed (R) $$\dot{R} = aI$$



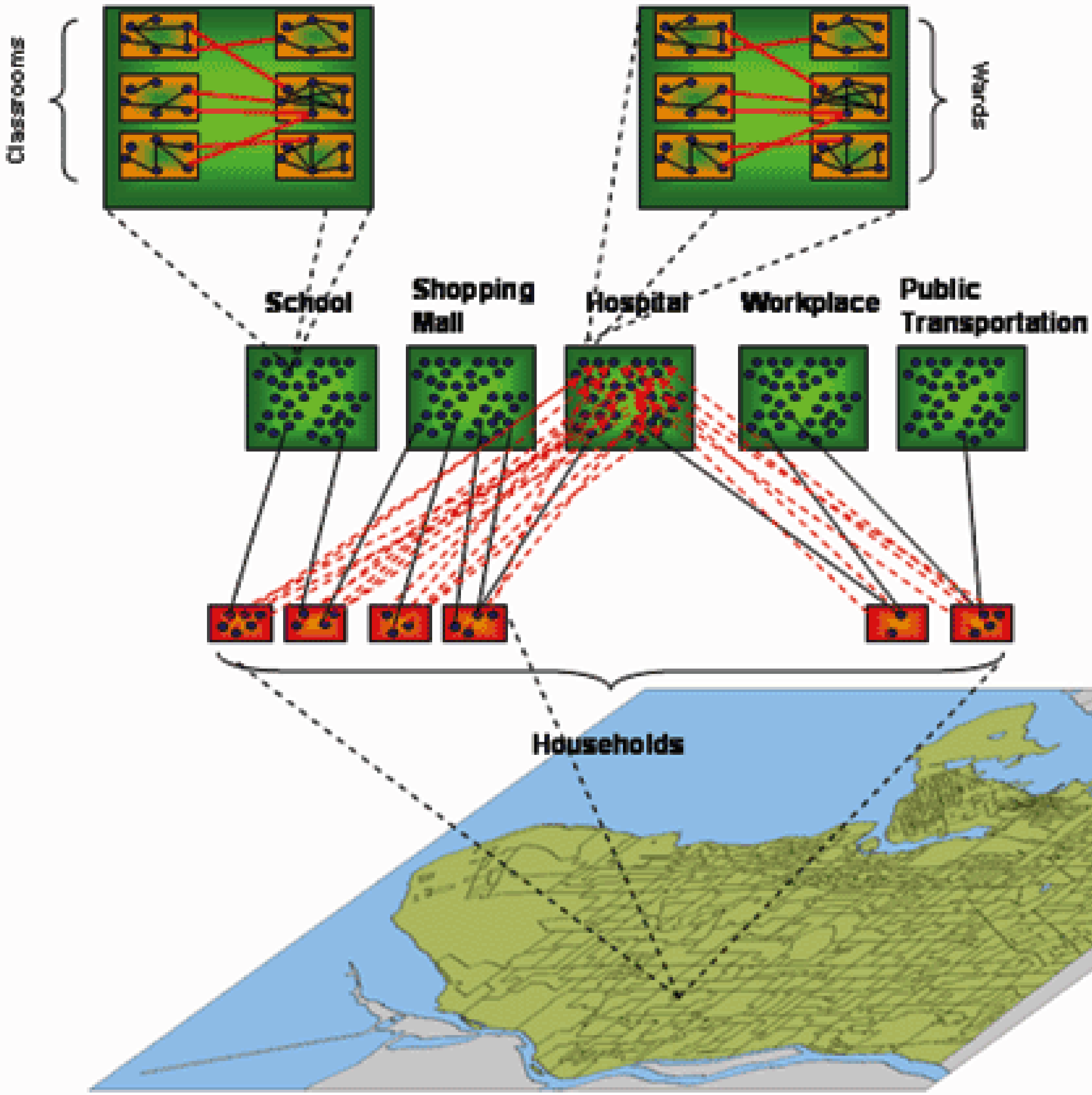


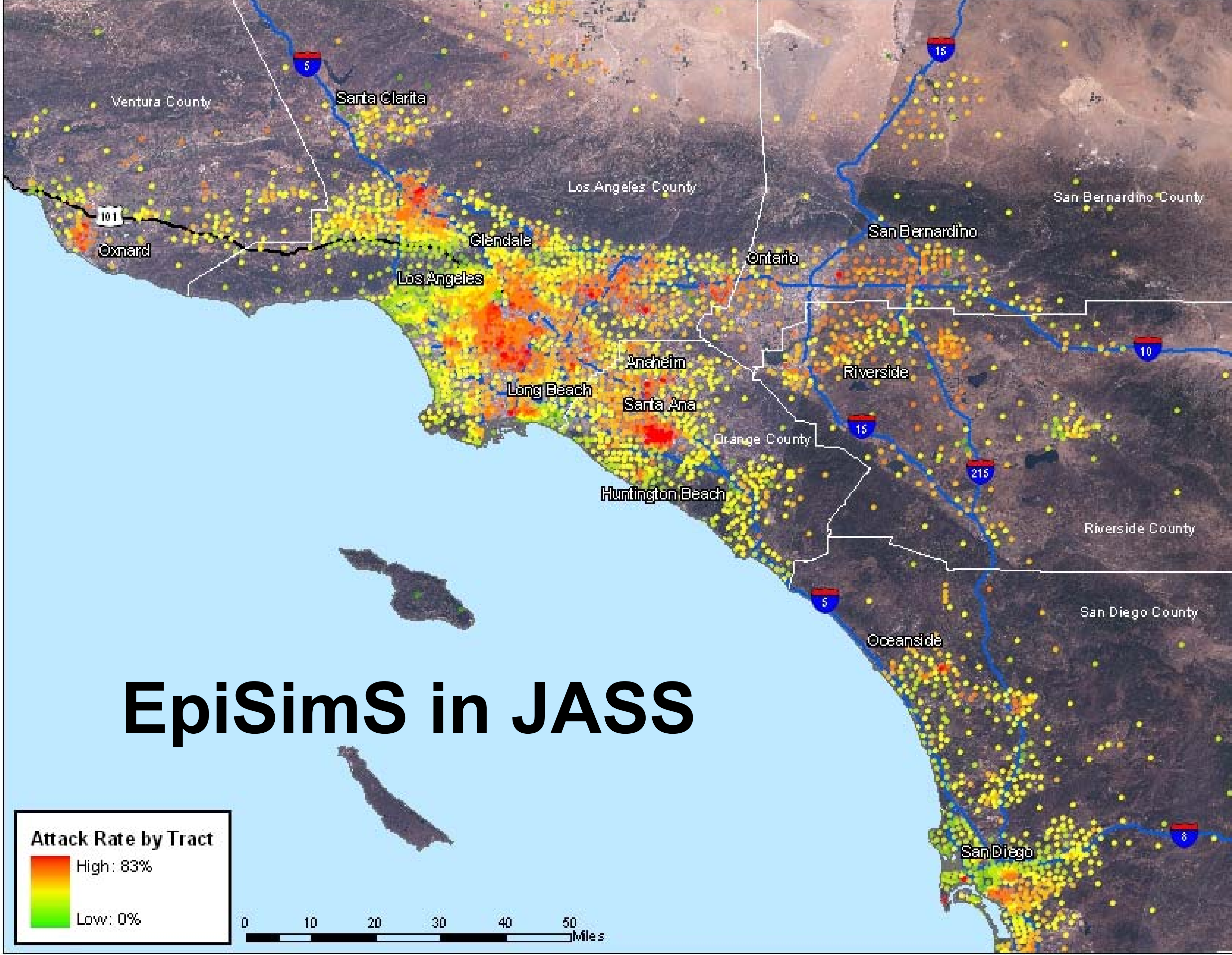


Barabasi's Nested Networks

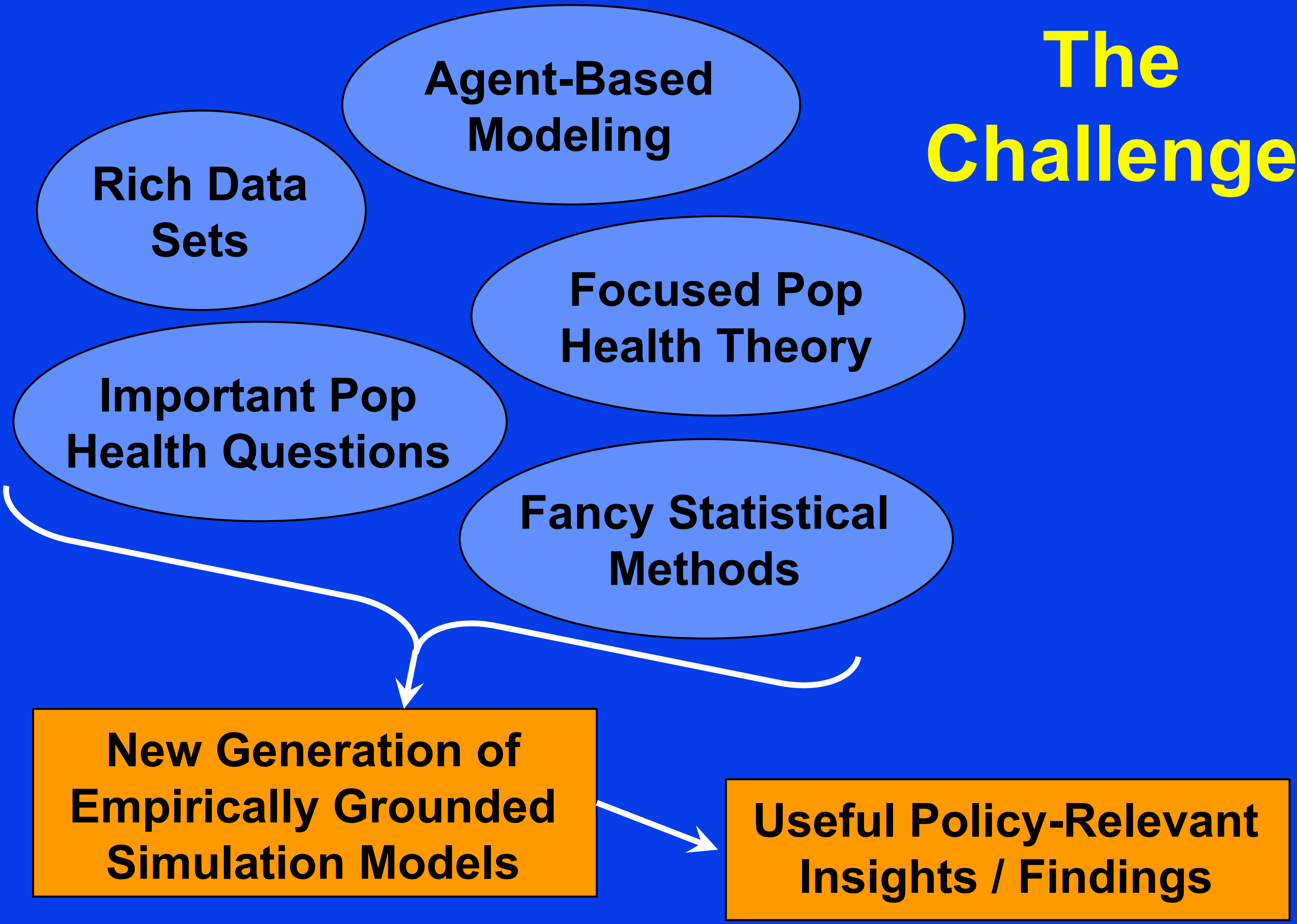
(commenting on Framingham "Friends" study re obesity)

Pourbohloul et al's Vancouver Network for Pandemic Flu Analysis




EpiSimS in JASS
Ventura County
Santa Clarita
Los Angeles County
San Bernardino County
San Bernardino
Glendale
Oxnard
Ontario
Los Angeles
Anaheim
Riverside
Long Beach
Santa Ana
Orange County
Huntington Beach
Riverside County
San Diego County
Oceanside
San Diego
Attack Rate by Tract
High: 83%
Low: 0%
0
10
20
30
40
50
Miles
5
15
101
10
215
8

The Challenge

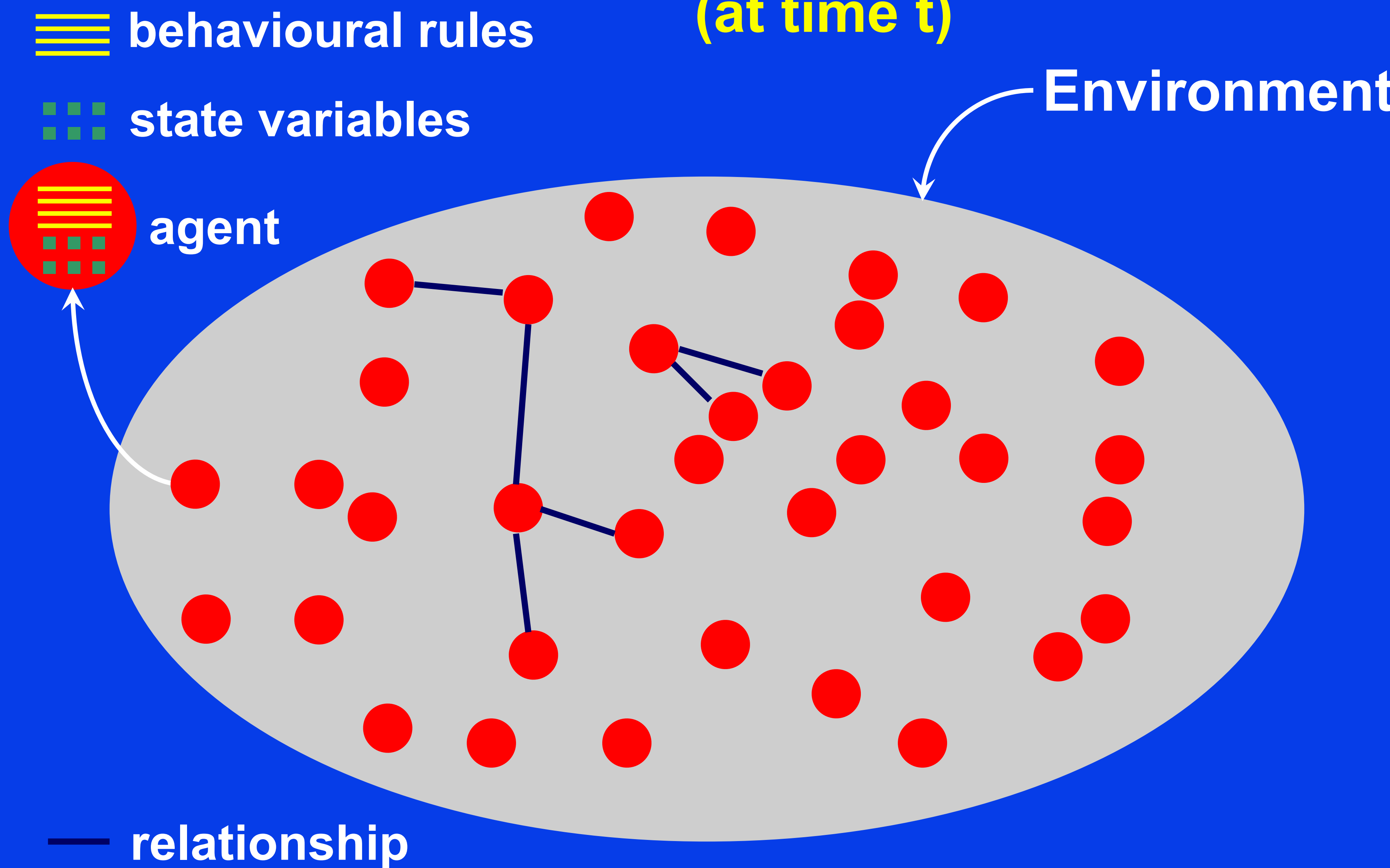


Meeting the Challenge

- build on existing efforts
- <u>extend</u>: "meta-synthesis" ≡ weaving together empirical results from studies of a diversity of topics (not just a single topic, as in meta-analysis)
- <u>bridge</u>: toy / theoretical ABMs (agent-based models) ↔ industrial strength policy-oriented microsimulation models
- <u>choose</u>: an intermediate scale of model
  - encompassing more than one of jillions of narrow foci; larger than current efforts
  - but not so much larger; ToE not on the table

Stylized Agent-Based Model

(at time t)



A Typology of Agent-Based Models

- agents' state variables and behavioural rules
  - toy / theoretical: no pretense of empirical basis
  - industrial strength: derived explicitly from data and analysis
  - n.b. actually a continuum, with use of "stylized facts" as an intermediate case
- agents' interactions with each other
  - none; evolve in isolation
  - interact re state variables only (e.g. infection)
  - interact re behavioural rules
  - n.b. static ↔ dynamic contacts
- the (rest of the) "environment" – hmmm!

Tales of Three Models

- Toy / Theoretical
  - Epstein et al., “Coupled Contagion…” model of pandemic flu
- Industrial Strength
  - HIVMM (=HIV Microsimulation Model) analysis of co-evolution of HIV and TB in South Africa (SACEMA, WHO and Statistics Canada)
  - POHEM (= POpulation HEalth Model) analysis of Rx preventive Tamoxifen

Epstein et al, “Coupled Contagion…”

S = susceptible
I = “infected”
R = removed / recovered
P = pathogen
F = “fear”

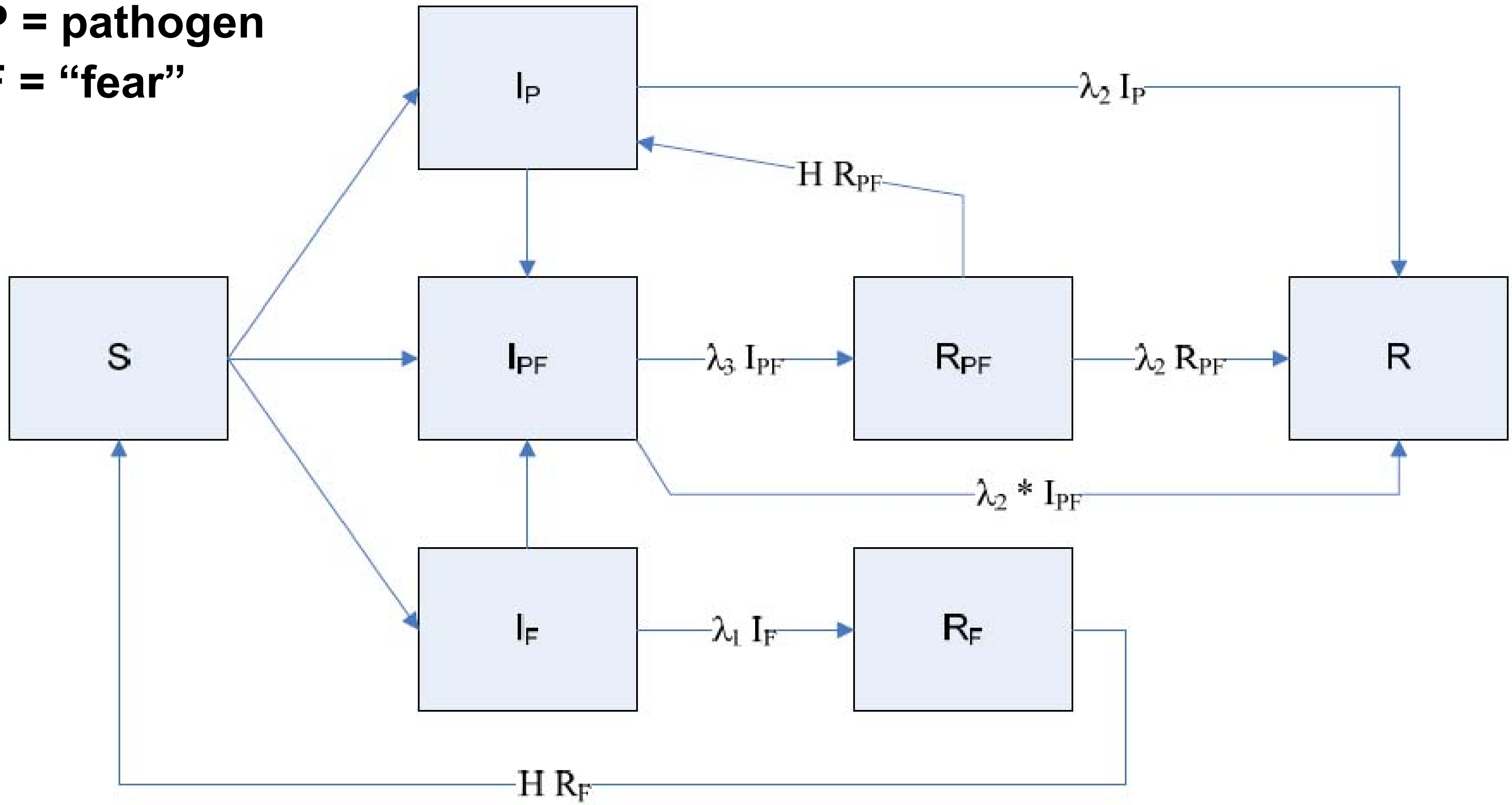


Figure 3: State transition chart.

Differential Equation Version of Epstein et al, “Coupled Contagion…”

$$\frac{dS}{dt} = -\beta(1-\alpha)SI_P - (1-\beta)\alpha SI_P - \beta\alpha SI_P - \alpha SI_F - \beta(1-\alpha)SI_{PF} - (1-\beta)\alpha SI_{PF} - \beta\alpha SI_{PF} + HR_F$$

$$\frac{dI_F}{dt} = (1-\beta)\alpha SI_P + \alpha SI_F + (1-\beta)\alpha SI_{PF} - \beta I_F I_P - \beta I_F I_{PF} - \lambda_1 I_F$$

$$\frac{dI_P}{dt} = \beta(1-\alpha)SI_P + \beta(1-\alpha)SI_{PF} - \alpha I_P I_P - \alpha I_P I_F - \alpha I_P I_{PF} - \lambda_2 I_P + HR_{PF}$$

$$\frac{dI_{PF}}{dt} = \beta\alpha SI_P + \beta\alpha SI_{PF} + \beta I_F I_P + \beta I_F I_{PF} + \alpha I_P I_P + \alpha I_P I_F + \alpha I_P I_{PF} - \lambda_2 I_{PF} - \lambda_3 I_{PF}$$

$$\frac{dR_F}{dt} = \lambda_1 I_{PF} - HR_F$$

$$\frac{dR_{PF}}{dt} = \lambda_3 I_{PF} - \lambda_2 R_{PF} - HR_{PF}$$

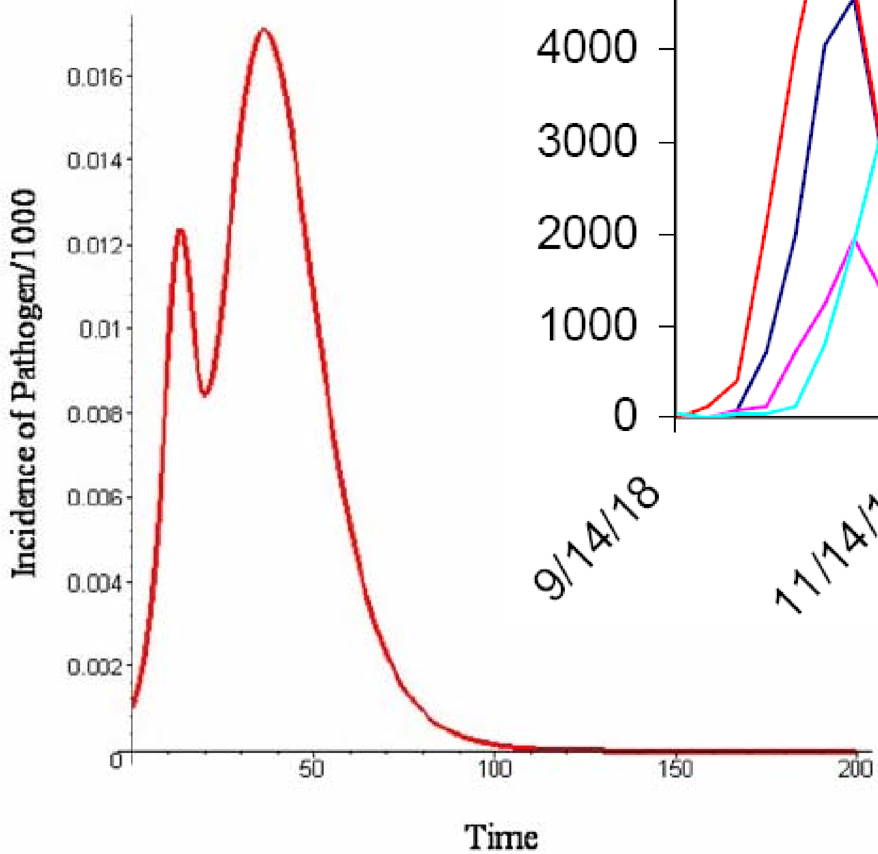
$$\frac{dR}{dt} = \lambda_2 I_P + \lambda_2 I_{PF} + \lambda_2 R_{PF}$$

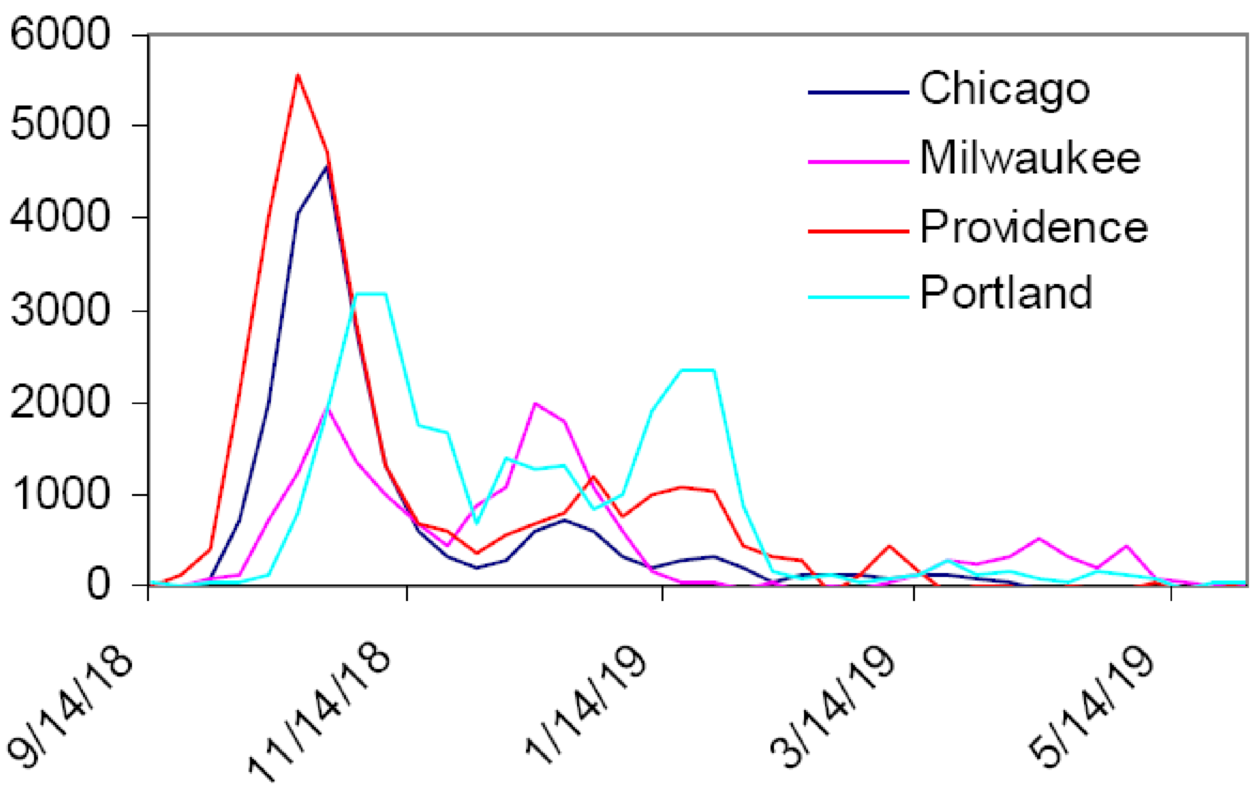
***Figure 4**: Classical SIR Differential Equations Formulation*

Agent-Based Version of Epstein et al, "Coupled Contagion…"

- "agents" live on a large "checkerboard"
- time unfolds in discrete steps
- state space as above – susceptible, "infected" (with either fear or pathogen or both), or removed
- seed the space with 1 infected at t = 0
- illness lasts 100, fear lasts 800, then spontaneous recovery
- agents move around randomly, and interact only with one of those closest at each time step
- watch the pathogen and fear spread, "in silico"

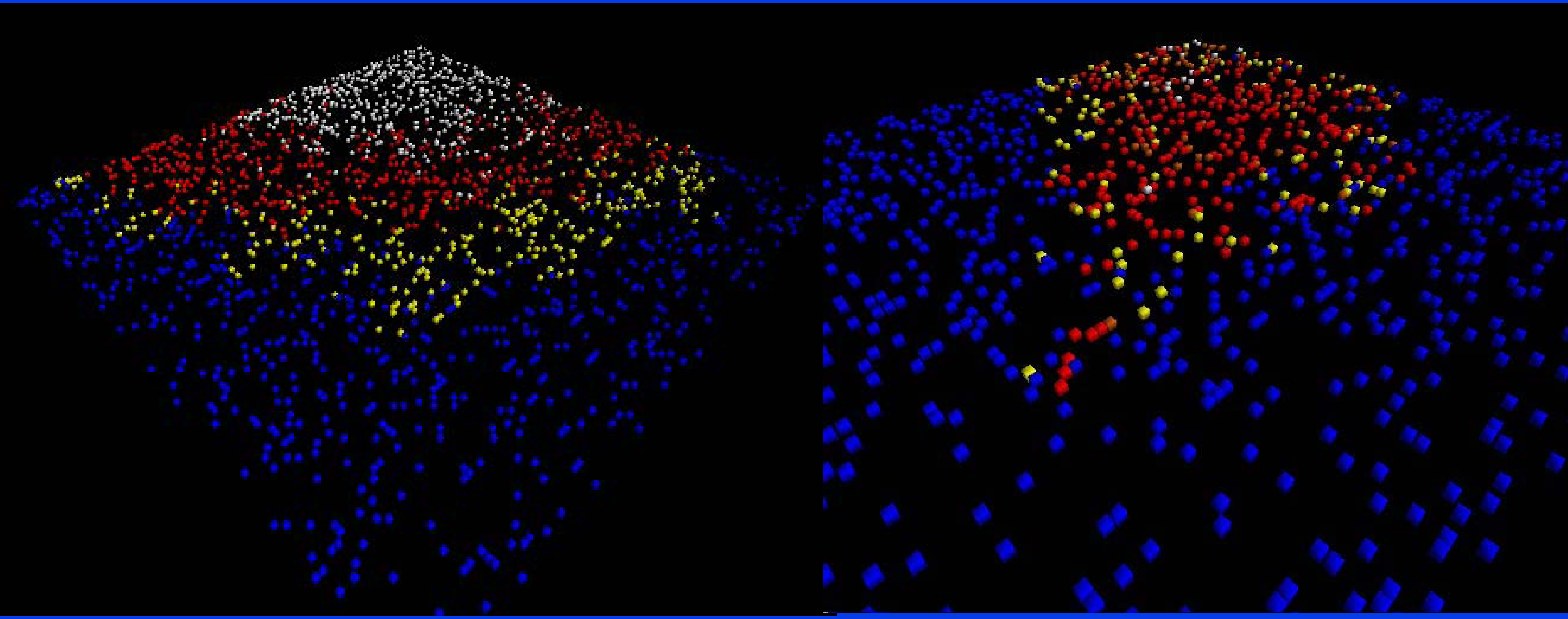
Coupled Contagion…
"Explain" vs "Account for"





Epstein et al, "Coupled Contagion…"

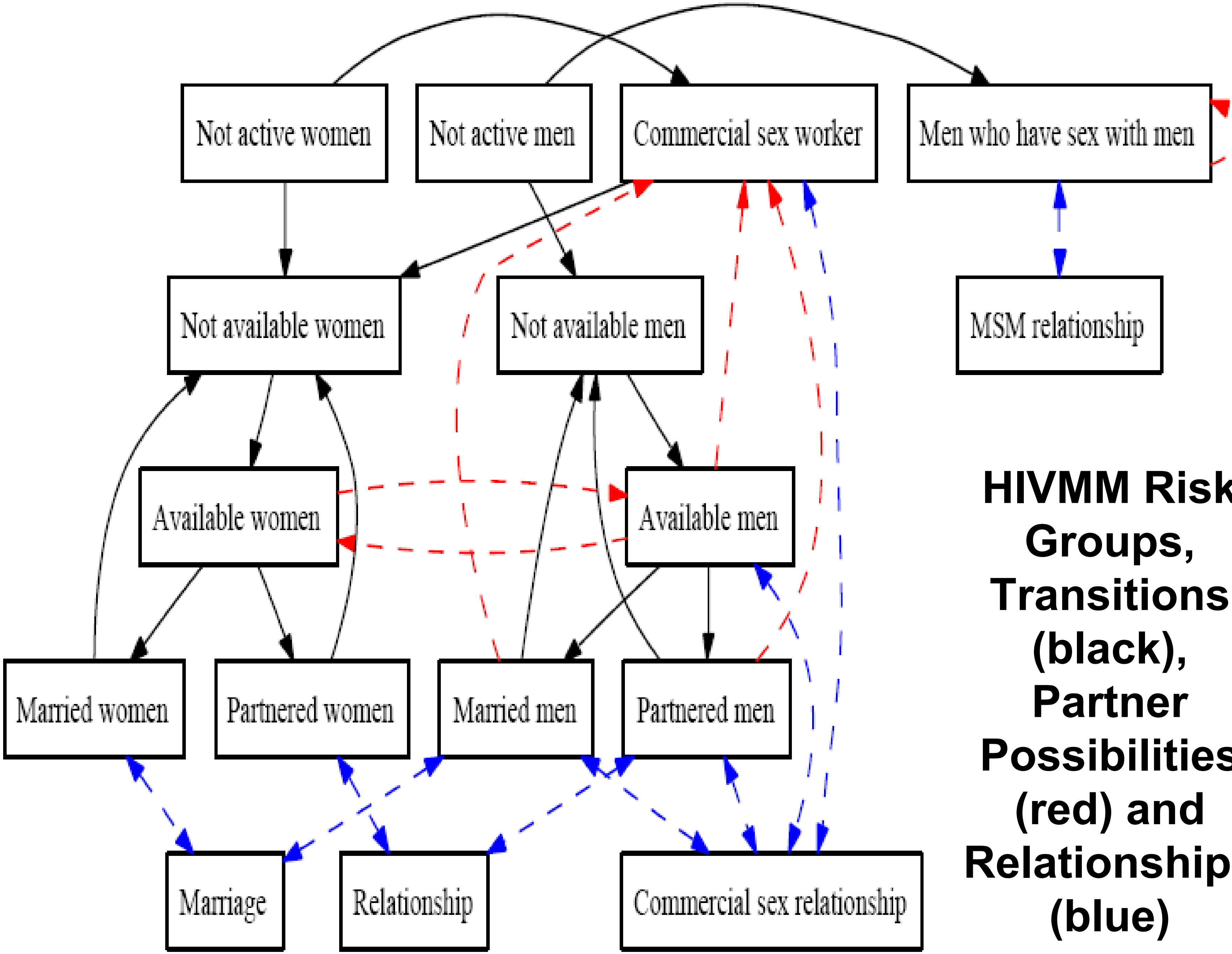
Screenshots from agent-based simulation model without and with flight. Each agent is represented by a colored dot on the lattice.



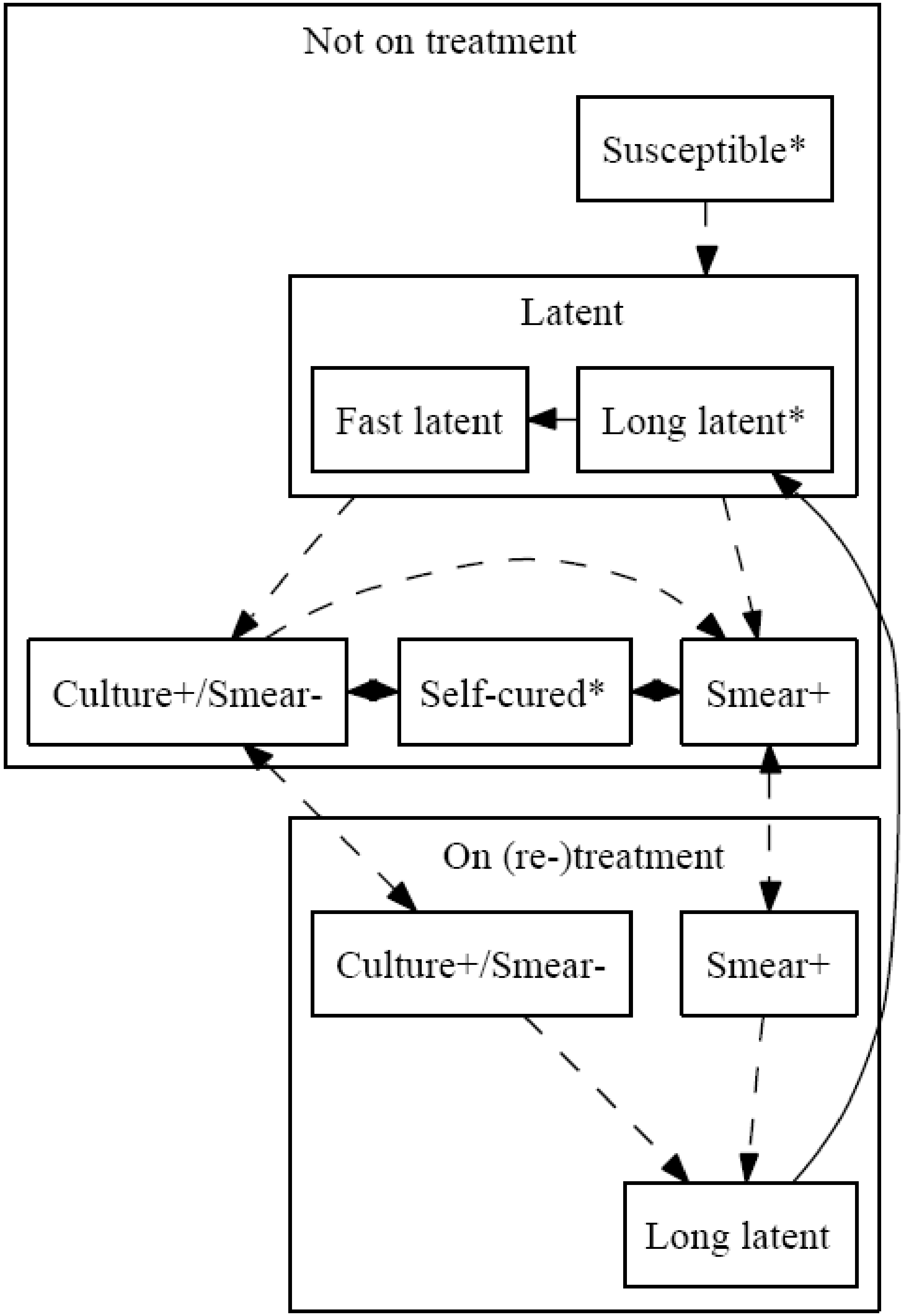
blue – susceptibles, no fear or pathogen
yellow – infected with fear alone
orange – acting on fear (right only, rare)
red – infected with pathogen
white – recovered

HIVMM – A Model of Co-Evolvoing HIV, STD and TB Infection in South Africa

- joint project of SACEMA, WHO and Stat Can
  - (funded by the Canadian International Development Agency)
- empirically grounded, policy-oriented
- agent-based, heterogeneous agents
- endogenous sexual contact network formation ⇒ “relationships” are explicit objects, just as are agents
- coupled TB, STD and HIV infection dynamics
  - HIV characterized by both stage and CD4
  - TB – susceptible, latent, culture & ~smear, smear
  - STD – GUD and non-GUD
- behaviours – condoms, ART, circumcision, …



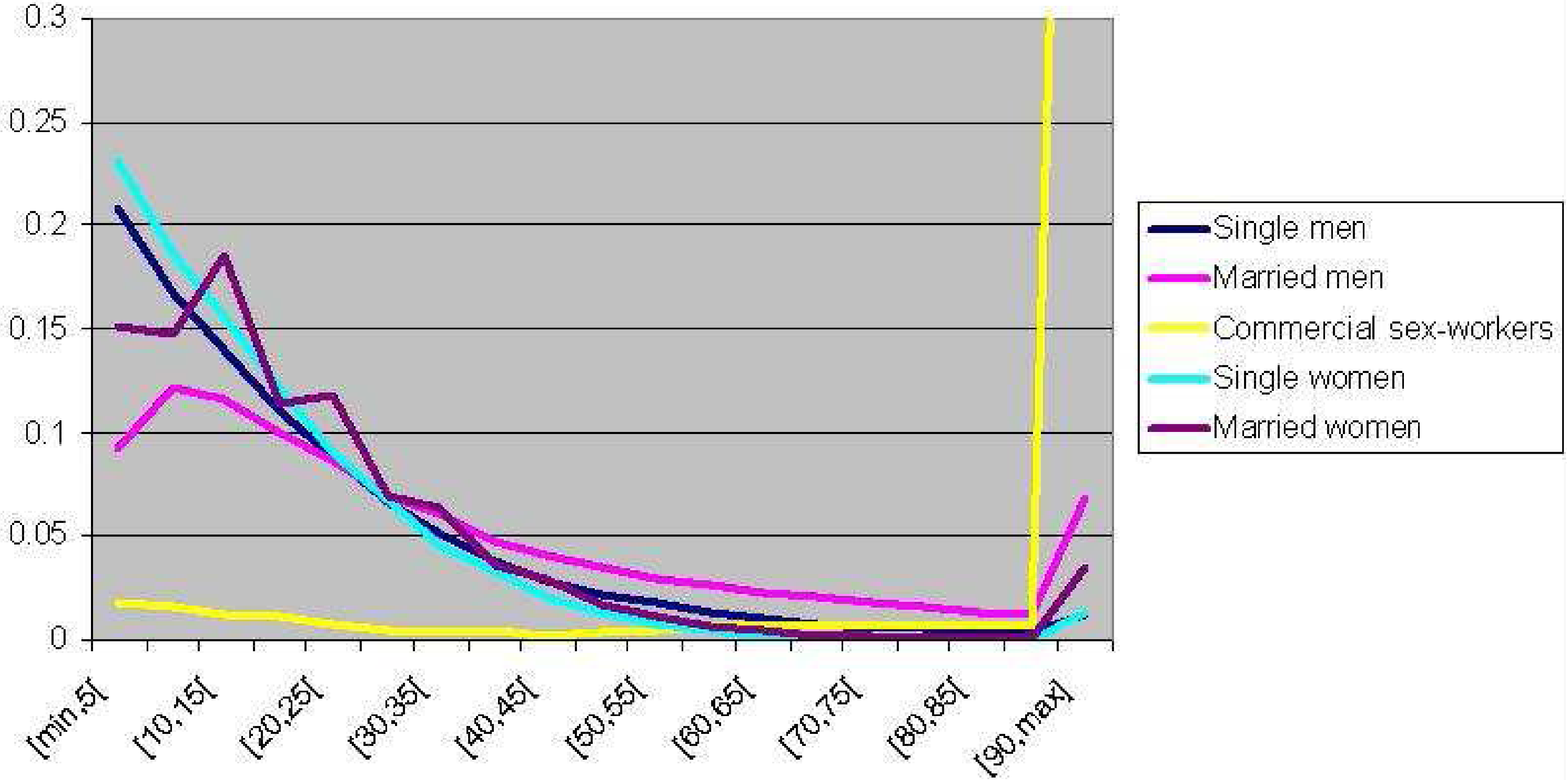
HIVMM Risk Groups, Transitions (black), Partner Possibilities (red) and Relationships (blue)

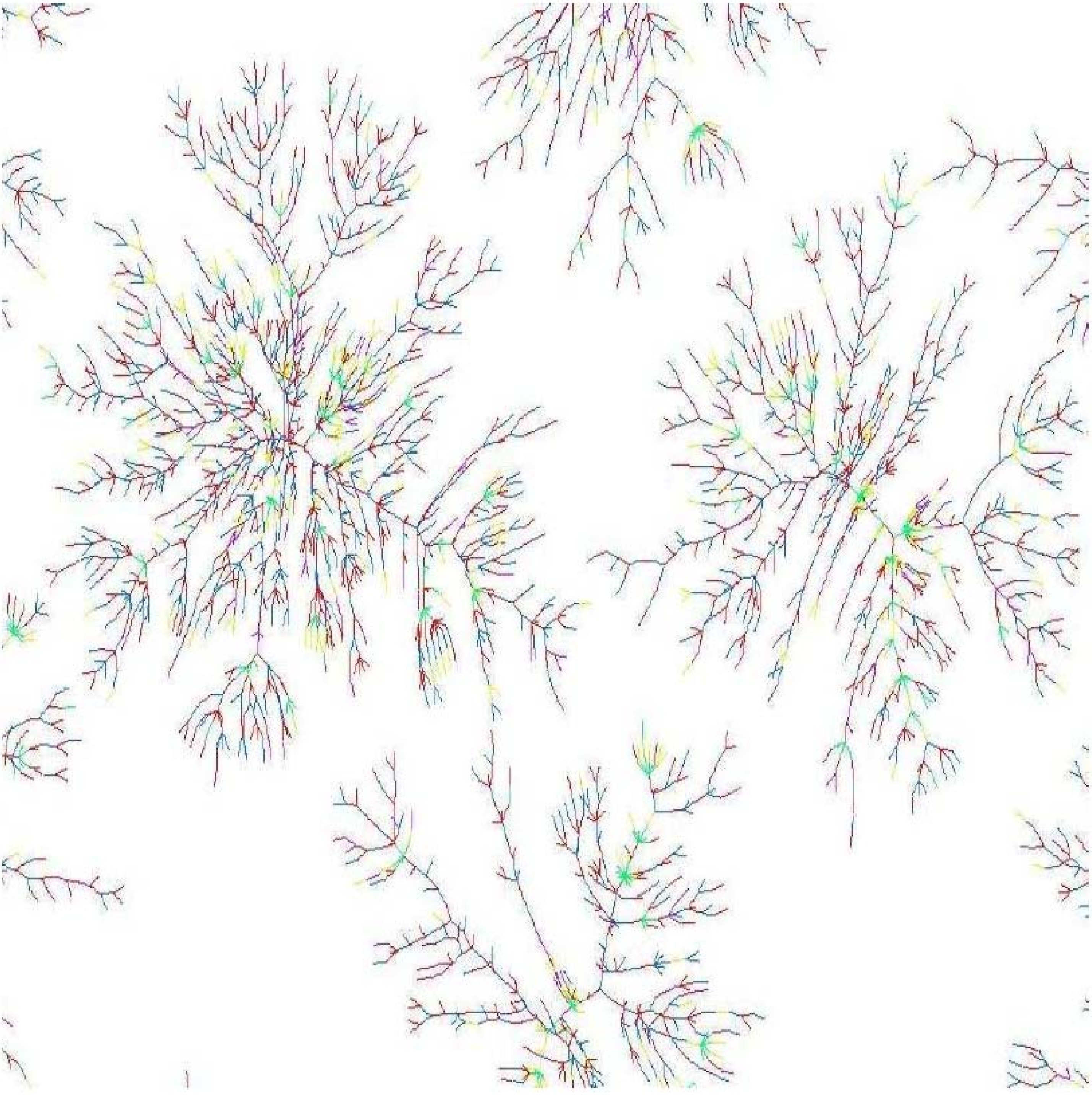


TB States and Transitions

- **dashed arrows indicate transitions affected by HIV status**
- **asterisks indicate states where contacts with others can affect TB status**

Distribution of number of partners by risk group





CSWs (green) often at root of HIV infection trees - HIVMM

Statistics Canada's POpulation HEalth Model (POHEM)

- using longitudinal Monte Carlo microsimulation
- starting from an actual representative population sample
- to synthesize a large sample of realistic, albeit synthetic, individual biographies
- using detailed data drawn from myriad sources – longitudinal (to the extent possible)
- to construct empirical statistical descriptions
- of risk factors, relative risks, disease incidence, disease progression, treatments, and mortality
- (but agents are not adaptive, not interacting – YET!)
- technically: multi-factorial, time-varying covariates, event history framework in continuous time, with competing risks and explicit comorbidity, and possibility to represent occult heterogeneity

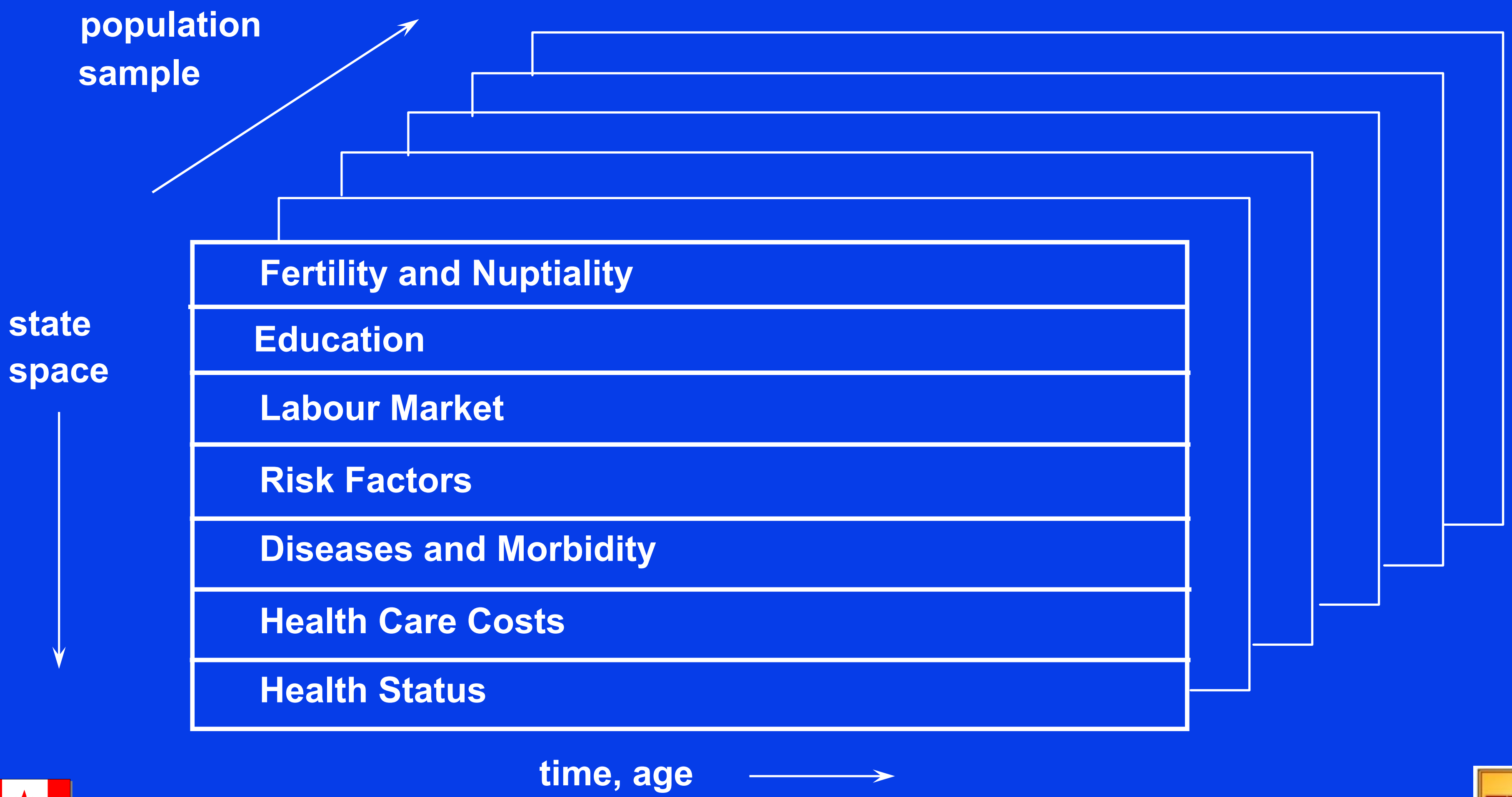
Population Microcosm for a POHEM Simulation

state space ↓

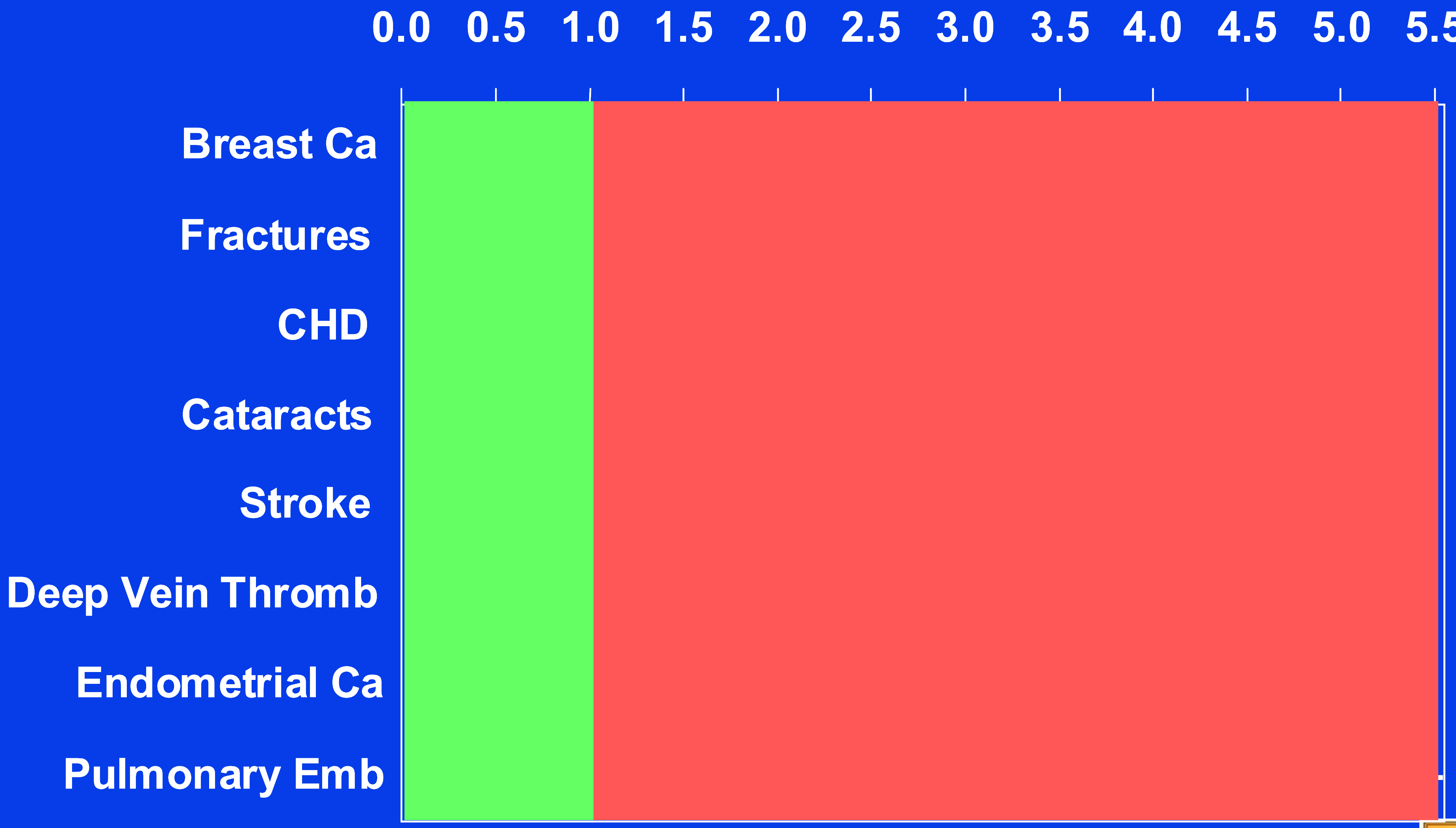
Fertility and Nuptiality
Education
Labour Market
Risk Factors
Diseases and Morbidity
Health Care Costs
Health Status

time, age →

Population Microcosm for a POHEM Simulation



Extrapolation to Canadian Women: Clinical Trial of Preventive Tamoxifen



J National Cancer Institute, 1999

Data Sources

National Breast Screening Study

Risk Factors

Incidence

Canadian Cancer Registry

Provincial Cancer Registries

Stage, Diagnosis and Treatment

Questionnaires to Oncologists

Disease Progression

Follow-up

Direct Costs

Ontario Health Insurance Plan

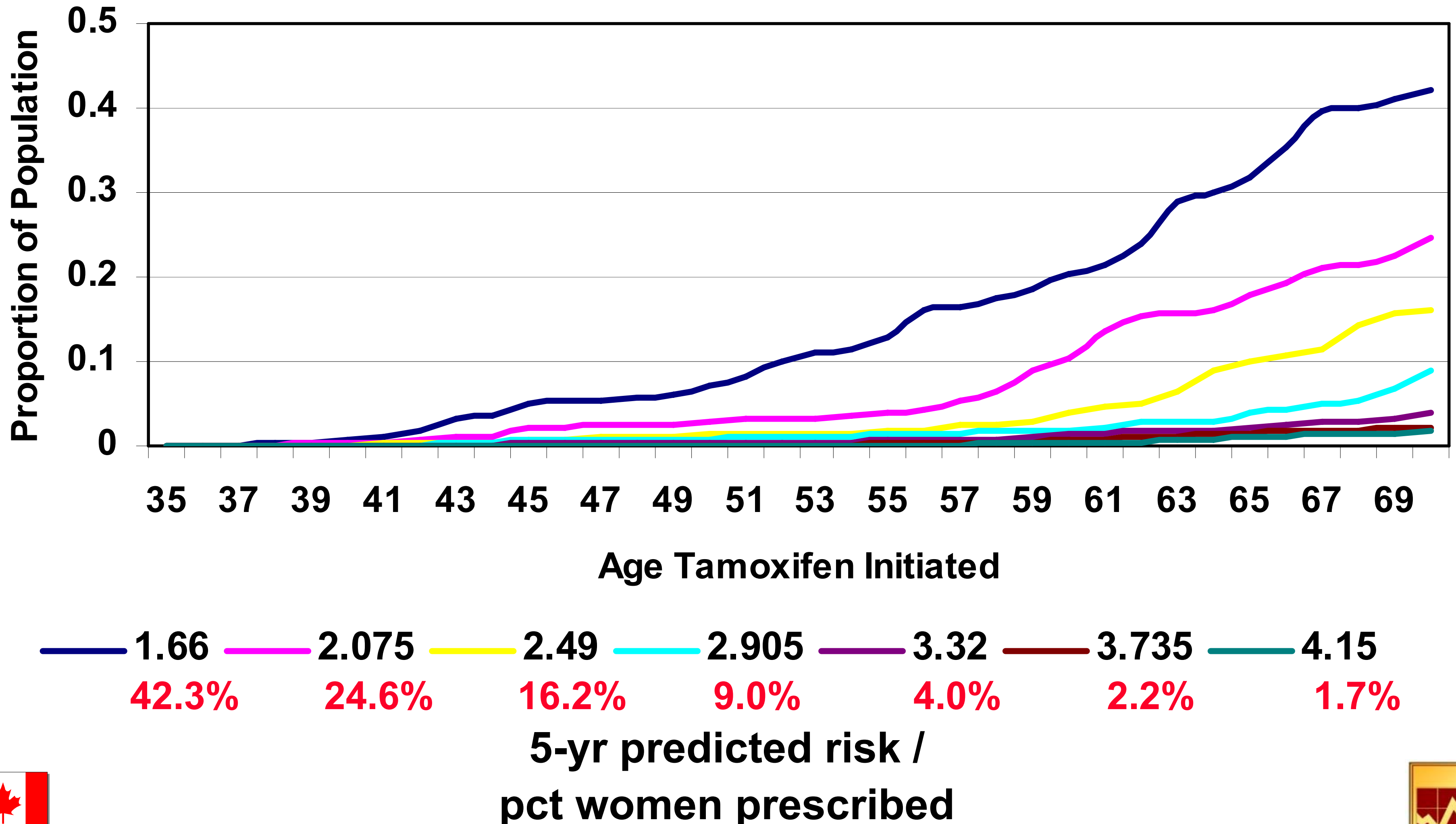
National Length of Stay Data

Canadian Institute for Health Information

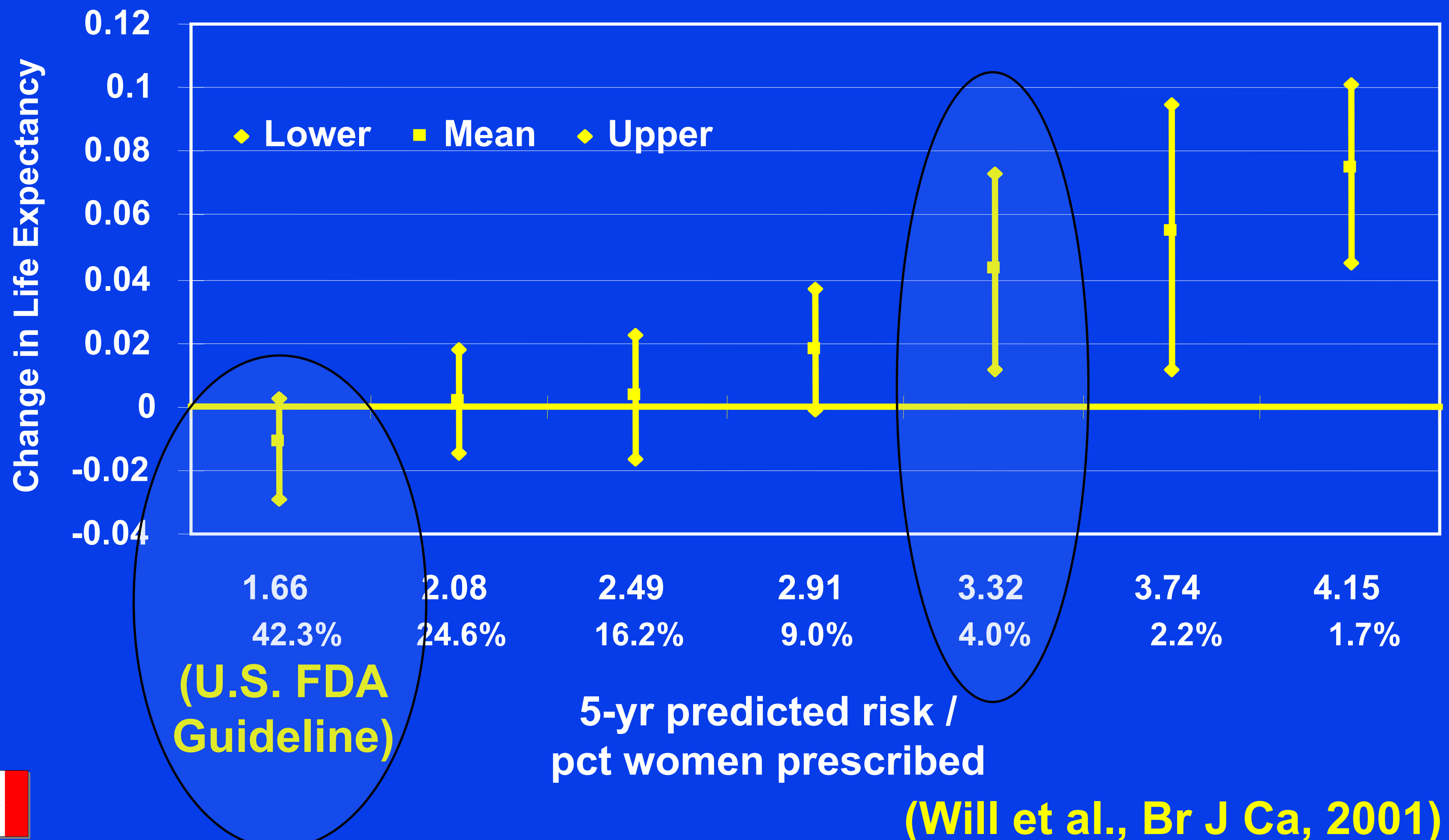
Who Should Take Tamoxifen?

- Ideally, persons who would get breast cancer
  - no perfectly predictive test exists to select persons who will get breast cancer
  - so select persons at "high risk" for breast cancer
- FDA approved label emphasized "high-risk"
  - at least age 35 with a 5-yr predicted risk of breast cancer of at least 1.67% using Gail's Algorithm

Up to 42% of Canadian Women Will Meet the FDA Guidelines for "High Risk"

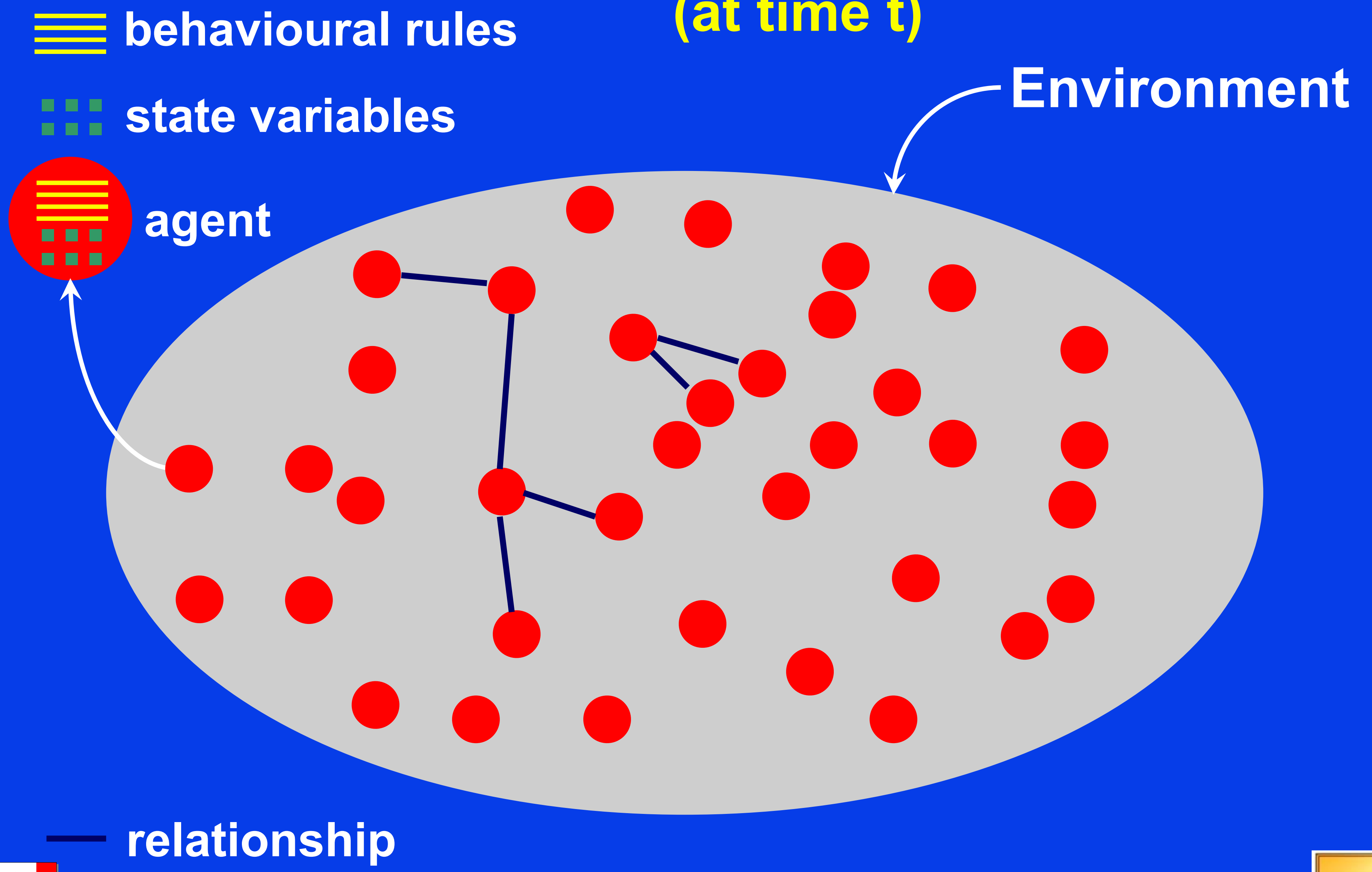


POHEM: Projected Changes in Life Expectancy for Canadian Women if Preventive Tamoxifen Prescribed per Various Risk Thresholds (Do No Harm?)



(Will et al., Br J Ca, 2001)

Stylized Agent-Based Model
(at time t)



Concluding Comments

- intriguing opportunities for cross-fertilization
  - complex systems theory / agent-based (toy = theoretical) models, and
  - industrial strength, policy-oriented, population health (and social policy) models
- depends critically on
  - more powerful longitudinal micro data sets
  - new kinds of compute intensive statistical methods
  - relevant social and health science
  - new (university-based?) research structures
    - large multi-skilled multi-disciplinary teams (compare physics, genomics)
  - to characterize agents' behavioural repertoires