In-Host Out-Host Interaction Models

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L.V. Anderson on Slate

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Its not just that a lot of people don't like the way latex condoms feel. They also don' t use them. In the 2010 National Survey of Sexual Health and Behavior, the largest-ever nationally representative sexuality study, . . . Adults who'd had anal sex in the past year—the highest-risk sexual act with regard to HIV transmission—said they'd used condoms only 20 percent of the time. . . . As Ron Frezieres, a Gates grantee who has designed and executed clinical contraceptive trials for more than 30 years, says, Even if a condom had twice the breakage rate but everybody loves it, it enhances sexmaybe that's really incredible, to get 100 percent product utilization of a product that breaks 2 percent [instead of] a 50 percent utilization of a condom that breaks 1 percent.

In-Host Basic Model

- x healthy cells, y infected cells, v virions
- Infection comes from initial conditions

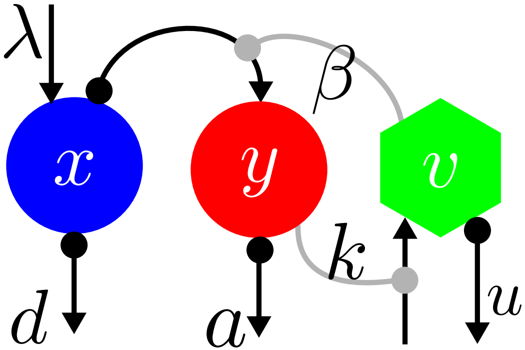
Basic Model

$x(0) = \frac{\lambda}{d}, \;\; y(0) = 0, \;\; v(0) > 0$

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv \\ \dot{y} &= \beta xv - ay \\ \dot{v} &= ky - uv \end{aligned}$$

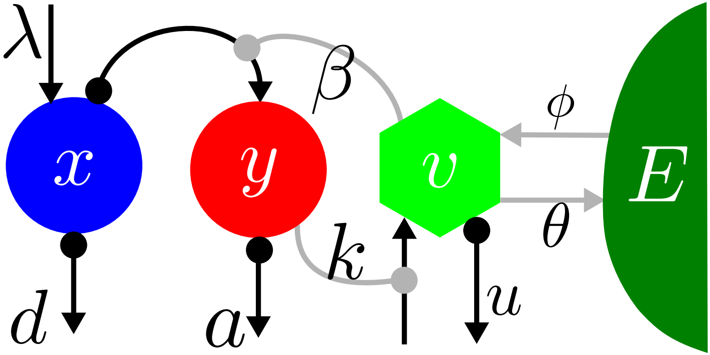
Infection persists if $R_0 = \frac{\beta \lambda k}{adu} > 1$

In-Host Basic Model



$$
\begin{aligned}
\dot{x} &= \lambda - dx - \beta x v \\
\dot{y} &= \beta x v - a y \\
\dot{v} &= k y - u v
\end{aligned}
$$

In-Host Model with Environmental Infectious Agent



$$\dot{x} = \lambda - dx - \beta xv$$

$$\dot{y} = \beta xv - ay$$

$$\dot{v} = ky - uv + \phi(E)$$

Coupling Model to Out-Host Interaction

Your textblock

Feng et al CITE for Toxoplasma-like disease

Two modified basic models:

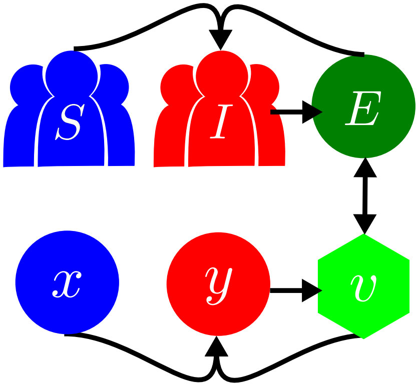
A In-Host

1. x healthy cells
2. y infected cells
3. v infectious agent

B Between-Host

1. S susceptible population
2. I infected population
3. E environmental contamination level

Timescales separate models



Between-Host Model

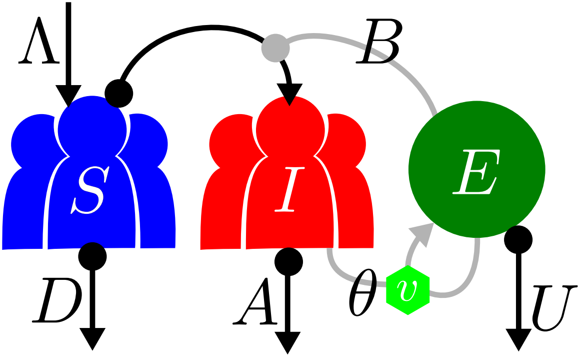
- S Suseptible individuals, I infected individuals, E environmental contamination %

Between-Host Model

$S(0) = \frac{\Lambda}{D}, \;\; I(0) = 0, \;\; E(0) > 0$

$$\dot{S} = \Lambda - DS - BES$$
$$\dot{I} = BSE - AI$$
$$\dot{E} = \theta(v)I(1 - E) - UE$$

In-Host Model with Environmental Infectious Agent



$$\dot{S} = \Lambda - DS - BES$$
$$\dot{I} = BSE - AI$$
$$\dot{E} = \theta(v)I(1 - E) - UE$$

Between-Host Reproductive Ratio

1. Decoupled Analysis
   i. Assume timescales decouple in long term
   ii. Out-host reproductive ratio controls if infection or virus free equilibrium is the attractor

$$R_{0\mathcal{O}} = \frac{\theta v \beta \Lambda}{DAU}$$

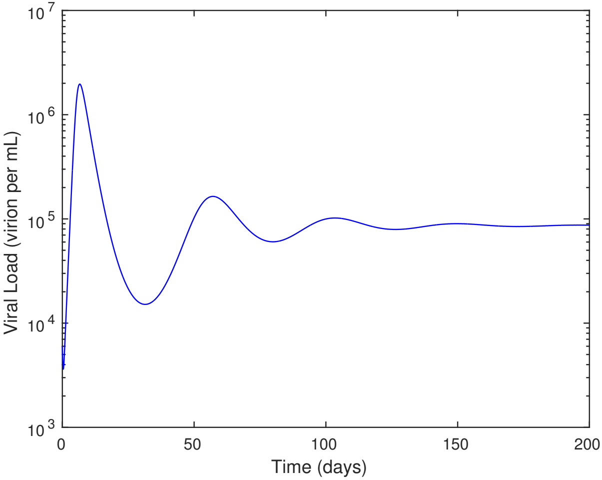
   iii. $R_{0\mathcal{O}} < 1$ environment clears R_0 plays usual role
2. Coupled Analysis
   i. Backwards bifurcation: $R_{0\mathcal{O}} > 1$ then the environment can sustain infections with $R_0 < 1$

Inapplicability to HIV

1. HIV does not persist outside of a host
   1. Can we reinterpret environment contamination as high risk sexual behavior/drug use?
2. All individuals are at the same stage of infection
3.

In-Host Viral Evolution

Parameters from CITE



Nested SI model

Your textblock

CITE

1. S susceptible individuals
   1. fixed birth rate
   2. proportional death rate
2. I infected individuals
   1. track infection age $I(a,t)$
   2. $\beta(a)$ transmission rate depends on infection age
   3. $\alpha(a)$ death rate depends on age
3. β and α determined by in host basic model

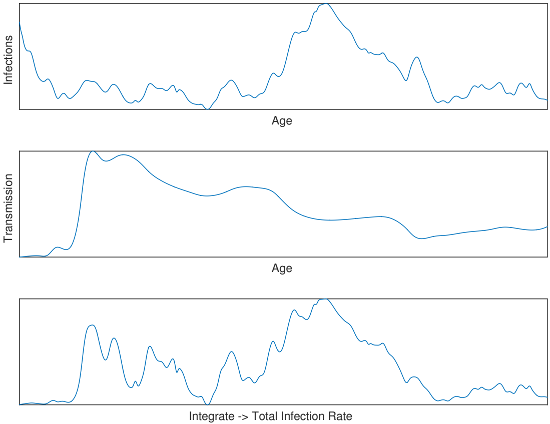
$$\dot{S}(t) = \lambda - dS - S\int \beta I \; da$$

$$I(t,0) = S\int \beta I \; da$$

$$\frac{\partial}{\partial t} I(t,a) = -\left(\frac{\partial}{\partial a} + \alpha(a)\right) I(t,a)$$

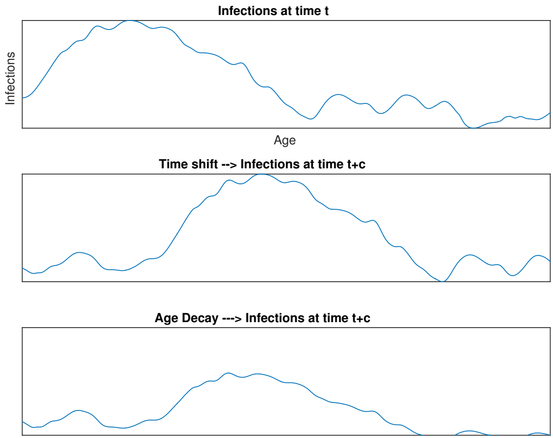
Population Infection Rate

Infection Rate $= \int I(a)\beta(a)\ da$



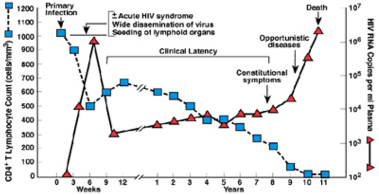
Population Infection Rate

$$\frac{\partial}{\partial t} I(t,a) = -\left(\frac{\partial}{\partial a} + \alpha(a)\right) I(t,a)$$



Nesting SI with basic HIV model

1. In-host model determines $\beta(a), \alpha(a)$
   1. Transmission $\beta(a) \propto v(a)$ proportional to viral load
   2. Death rate...
      1. proportional to $\int y da$?
      2. Requires in-host model that explains 10 year death
2. Viral evolution
   1. Parameters may be time dependent



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

Inapplicability to HIV

1. Transmission events are time discretized
    1. Viral load evolution is on the timescale of days-weeks
    2. Transmission events are on a similar timescale relatively brief with high infectivity
2. HIV is highly dependent on network geometry

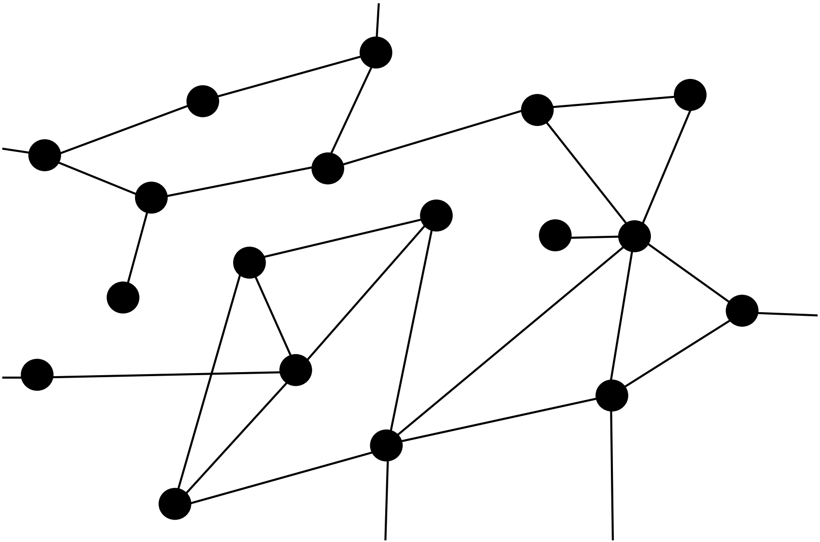
Stochastic In-Out Model

Incorporate geometry and discrete exposure:

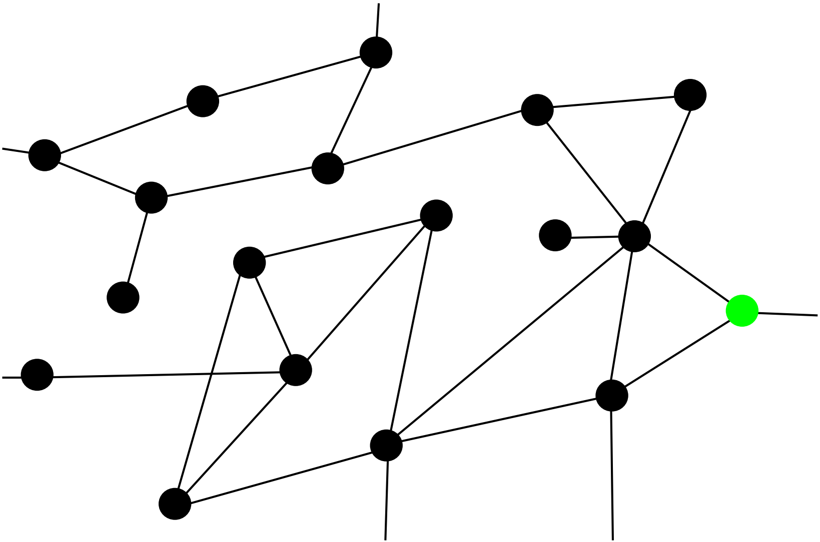
A Stochastic Model

1. Graph $\Gamma = (V, E)$
2. Vertices are individuals equipped with in host model.
3. Exposure events occur as a Poisson process on edges.
    1. at exposure virtices exchange virus proportional to current viral load
    2. between exposure events system evolves as independent in-host models

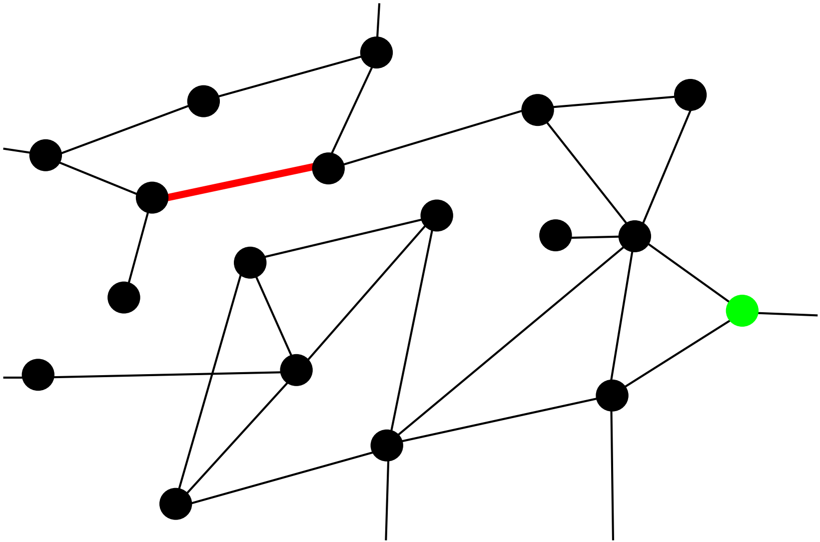
Stochastic In-Out Model



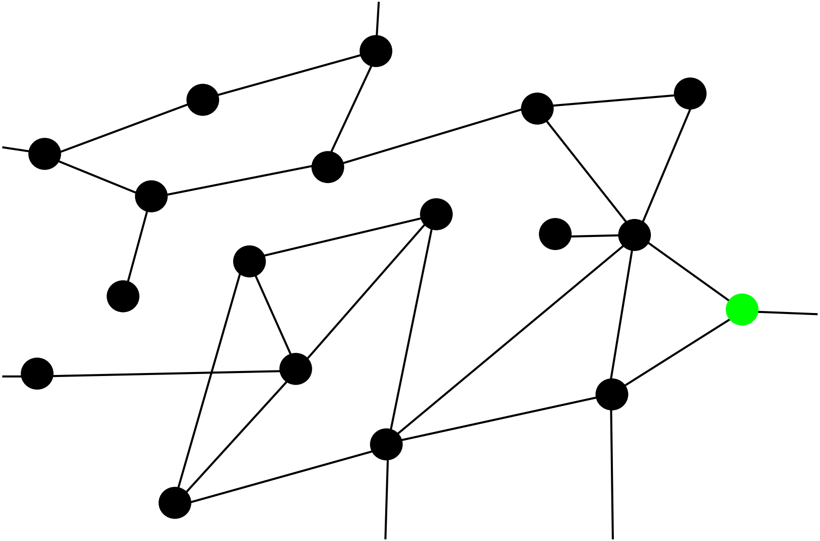
Stochastic In-Out Model



Stochastic In-Out Model



Stochastic In-Out Model



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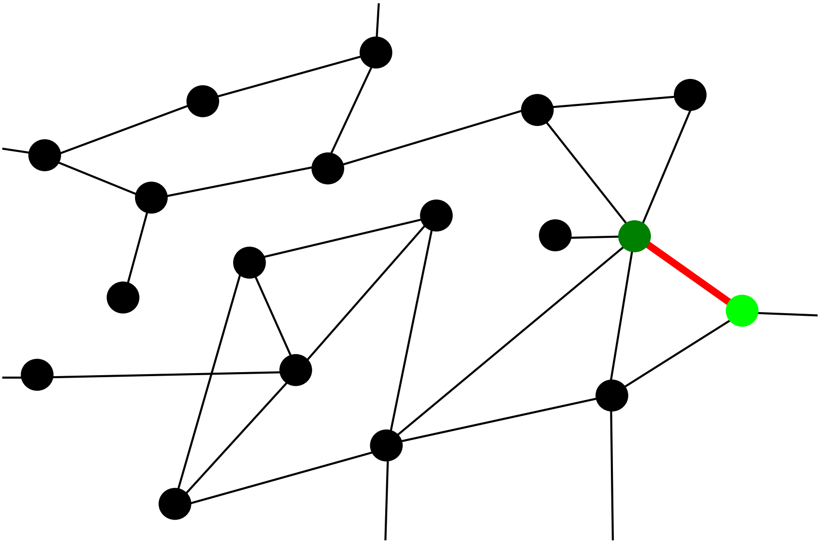

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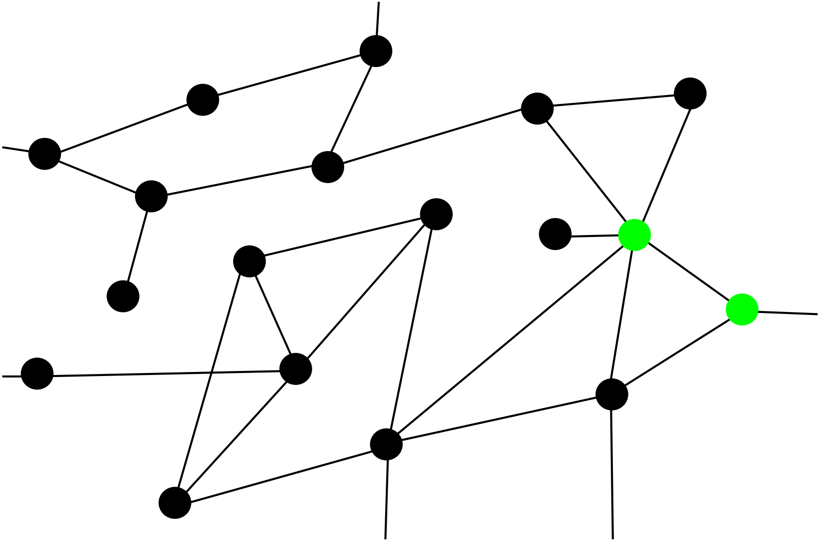

Difficulties and Benefits

Con

1. Requires geometric information
2. Requires detailed data on sexual habits
3. Analysis requires stochastic calculus

Pro

1. Easy to implement
2. More obviously implements the reality of HIV transmission
3. Allows study of condom usage, PrEP, behavior

Questions

1. Are there non-total-infection stable equilibria for connected Γ?
2. If Γ is a complete graph does the Stochastic model reproduce Nested SI model behavior in the limit? what is the appropriate limit?
3. Does the model display multiple infection or backwards bifurcation for highly connected Γ or high rate of transmission events?
4. How influencial is Γ geometry in determining infection rates? What notions of graph theory indicate fast infection?
5. How can you distribute PrEP vertices to slow infection spread?
6. (Gates Question) What quantitative effect does an inferior but frequently used condom have on transmission?

L.V. Anderson.
We should have a better condom by now. heres why we dont.
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