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Quantifying the Impact of Two Pinning Control Strategies on HIV Incidence ⋆

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Abstract: The ability to quantify the impact of interventions in disease management is important from a public health perspective. The impact of two local control strategies are explored for a scale-free sexual contact network. The network is used to model the spread and incidence of HIV and subjected to pinning control of nodes at random and thereafter selectively pinning nodes with the highest degree. Infections are dependent on a stochastic function to capture the discrete nature of infections. New cases of people that have acquired the Human Immunodeficiency Virus (HIV) in the network are measured over a period of a year and also over a period of 5 years, with the pinned nodes controlled from the moment they get infected. Measurements are compared between pinning control schemes and to the uncontrolled scenario. The resulting comparisons indicated that selective pinning reduced the incidence in a large network (>1000 nodes) by at least 68%, compared to random pinning. This result is consistent with selective pinning control schemes employed in other scale-free dynamical networks.

1. INTRODUCTION

A substantial volume of work is available that describes the epidemiology of disease through complex network modelling (Xiao [2002], Tuckwell et al. [1998] and Shi et al. [2008]). In particular, the modelling of the spread of HIV infection has been presented by Sloot et al. [2008]. From a control-systems perspective, advances have been made to evaluate the impact of applying local control to nodes of a complex network in a structured manner (Wang and Wen [2008]), deemed "pinning control". Given this, a lack of published work exists that describes the impact of a pinning control scheme on an HIV-infected disease network. In this work, nodes will be locally controlled using the application of Reverse Transcriptase Inhibitors (RTIs) as prophylaxis to limit the spread of infection. RTIs, and in particular Tenofovir, has been shown to yield a maximum efficacy of around 80% if used daily (Duwal et al. [2012]).

Existing methods for analysing disease networks focus on the structure of a network as approximation to real-life disease networks (Keeling and Eames [2005]). By varying networks from randomly connected nodes to completely "scale-free" and comparing the behaviour of disease-spread through the variety of networks, it has already been ascertained which network type corresponds to known epidemiologically modelled populations (Danon et al. [2011]). It has indeed been determined that, with particular relevance to HIV, that human networks of sexual contacts are inherently "scale-free" (Liljeros et al. [2001]), which means that their cumulative degree-distribution follows a power-law of the form

$$P(k) \approx k^{-\alpha} \tag{1}$$

where $P(k)$ is the proportion of nodes in the network with k connections and α determines the decay in this proportion.

Given the type of network representing the spread of disease, the questions remains: What would be the impact on the number of new cases of HIV (incidence) in this network over a period of 1 year if local control of the virus with the prophylactic RTI Tenofovir is applied to a random selection of the nodes? And a further question: How would the impact change if the strategy of selection of the controlled nodes is changed to only be the most highly-connected nodes?

Together, these questions present a basis from which to quantify the effect of controlling an HIV network by controlling individual nodes. In this work, a hypothetical sexual network of individuals with HIV was examined. A selection of assumptions were made:

- Nodes in the network are homogenous and have identical HIV immune responses. The parameters from Table 1 apply to each node, except uninfected nodes which have an initial viral load of zero.
- The network is static, with all nodes participating throughout the observed time and none of the nodes leaving the network nor any nodes added
- Sexual relations occur on a continuous basis, and not discrete events

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- One node is infected to start the infection in the network. This node has an initial viral as indicated in Table 1.
- Sexual contact is assumed to be heterosexual, thus the network links represent a heterosexual network of sexual contacts
- Reinfection occurs after the first infection of a node
- Sexual relationships are not broken during the year of the simulation.
- Reverse transcriptase inhibitors are maximally effective at 80% (Duwal et al. [2012]) for each person

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2. MODELS AND CONTROL

2.1 3D model of HIV

For this work, each node's dynamics of the immune response to HIV *in-vivo* have been described by the three-dimensional model Nowak and Bangham [1996], Nowak and May [2001], with parameters estimated by Filter et al. [2005]:

$$\dot{T} = s - dT - \beta T v$$
$$\dot{T^*} = \beta T v - \delta T$$
$$\dot{v} = kT^* - cv \tag{2}$$

The states and parameters of the model represented by Equation 2 are shown in Table 1.

Table 1. States and parameters of the 3D model of HIV

State	Description	Value
T_0	Initial CD4+ count	1000 copies/ml
T_0^*	Initial infected CD4+ count	1 copy/ml
v_0	Initial viral load	100 copies/ml
Parameter	**Description**	**Rate (per day)**
s	Source of healthy CD4+	10.7
d	Death rate of CD4+	0.015
β	Rate of CD4+ infection	4.5×10^{-6}
δ	Death rate of infected CD4+	0.58
c	Death rate of free virions	2.05
k	Virus production rate	896.49

2.2 Network model

When this single-node immune response model is extended to form part of a network of individuals linked through their sexual partnerships and hence the possible transmission of HI virions, similar to the work done by Tuckwell et al. [1998], the viral load equation becomes:

$$\dot{v_i} = kT^* - cv + \zeta_i(t) \sum_{j \neq i}^{N} a_{ij} \Gamma v_j \tag{3}$$

In this equation, the matrix a_{ij} represents the network structure, hence it indicates which nodes are connected to node i. The matrix Γ represents the coupling of the viral load of this node to the viral node of the node's neighbours, v_j is the viral load of the node connected to node i.

2.3 Transmission function

The transmission of virions between the i-th node and the nodes connected to it is represented by $\zeta(t)$. In a real network of sexual contacts, which represents the main coupling method by which the virus is transferred (Royce and Sena [1997]), the per-coital-act probability of transmission of the virus in the case of African HIV-1-serodiscordant couples is modelled by Hughes et al. [2012], and denoted here as λ_v. The baseline risk of transmission is increased by numerous risk factors, of which the main two are the presence of multiple sexual partners and Herpes Simplex Virus (HSV-2) infection. This increase in likelihood of HIV infection is represented by R, a random number generated from a uniform distribution, using the range obtained in Arora et al. [2012]

$$\lambda_v = 1 - \left[1 - 9.36 \times 10^{-4}\right]^{e^{(.92 * log_{10}(v_j))}}$$
$$\zeta_i(t) = R \times \lambda_v \times \phi_v, \quad R \sim U(1, 6.44) \tag{4}$$

where v_j is the viral load (in copies per ml) of a sexual partner. The function λ_v is represented in (Fig. 1) and ϕ_v is the coupling-strength, or the actual amount of virus transferred between two nodes.

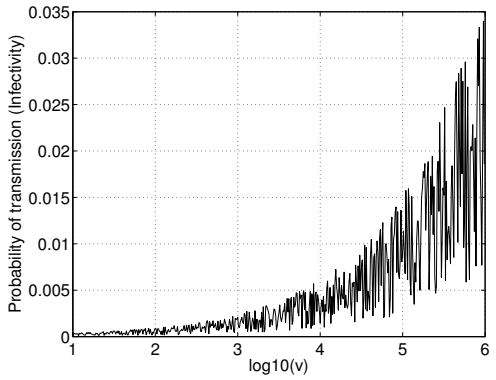

Fig. 1. ($\lambda_v \times R$) - Per-coital-act probability of viral transmission, with additional risk factors varied randomly across the population. This creates a band of infectivity at a particular viral load.

2.4 Local control

The approach of using anti-retroviral drugs as control inputs to an immune response model is not new and was effectively demonstrated by Jeffrey et al. [2003]. The difference with the work presented here is that an assumption is made that drugs are a continuous control inputs, rather than scheduled periodically (which is more realistic but chosen as such for simplicity). A control is applied locally to a selection of nodes. The control, which is the application of RTIs to a node, is represented as proposed by Perelson and Ribeiro [2013], preventing the infection of healthy CD4+ T-cells by the virus:

$$u_i = (-\varepsilon_{RTI})\beta v T \tag{5}$$

This means that the final controlled network model of HIV in this case is represented by:

$$\begin{aligned} \dot{T}_i &= s - dT - \beta T v + \Delta_i u_i \\ \dot{T}_i^* &= \beta T v - \delta T + \Delta_i u_i \\ \dot{v}_i &= kT^* - cv + \zeta_i(t) \sum_{j \neq i}^{N} a_{ij} \Gamma v_j \end{aligned} \tag{6}$$

Here, Δ_i is a function representing whether a node is controlled or not, of the form:

$$\Delta_i = \begin{cases} 1 : \text{node controlled} \\ 0 : \text{node not controlled} \end{cases} \tag{7}$$

For the random pinning control scheme, Δ_i would thus be equal to 1 for each one of the randomly predetermined percentage of pinned nodes in the network. For the selective pinning control scheme, Δ_i would be equal to 1 for each of one of the highest degree network nodes selected for control. In either control scheme, the specific percentage of pinned nodes was determined before the simulation commenced.

3. METHODS

An experimental scale-free network was set up to be able to note the effect of different pinning control schemes on the incidence of HIV in the network.

3.1 The network and pinned nodes

To establish a simulation of the network of sexually connected individuals, the node models of the network were firstly addressed. Each node is an individual with an immune response provided by Equation 2. Because it was assumed that all individuals in this network have the same immune response, the initial conditions and parameters for each node were chosen to be the same. Model parameters were obtained from Filter et al. [2005], and given as $\hat{\chi} = \{s;\ d;\ \beta;\ \delta;\ c;\ k\} = \{10.7;\ 0.015;\ 4.5 \times 10^{-6};\ 0.58;\ 2.05;\ 896.49\}$, with the initial conditions for an infected node given as $\overrightarrow{I_o}(t) = \{T_0;\ T_0^*;\ v_0\} = \{1000;\ 1;\ 100\}$. It should be noted here that only 1 node was randomly chosen to be infected at the start of a simulation, and that the initial conditions for all other nodes were $\overrightarrow{U_o}(t) = \{T_0;\ T_0^*;\ v_0\} = \{1000;\ 0;\ 0\}$.

For nodes that were pinned (people that were given RTIs), the term u_i was added as indicated in Equation 6. The value of ε_{RTI}, which is the effectiveness of prophylactic RTI treatment, was chosen to be 70% for all individuals in the network, which is close to the maximum protection of 80% noted in the trial results of Duwal et al. [2012].

A network was set up with an arbitrary set of 1000 nodes. The nodes were connected to resemble a scale-free network, with $\alpha = -2.4$ as found from a random sample of people by Liljeros et al. [2001]. This exponent of Equation 1, for the particular simulation presented here, represents an average node degree distribution of approximately 3 partners per person. The network is also 100% reciprocal, which means that the probability of viral transmission is bidirectional between any two connected nodes. A summary of the network used in all simulations is given in Table 2.

The transmission of virus between any two nodes are thus dependent on the following list of conditions:

- (α) - Whether the nodes are connected to begin with, thus network architecture implying a sexual relationship between the nodes
- (λ_v) - The probability of transmission given the viral load of either partner
- (R) - The increased risk of transmission given the distribution of additional risk factors in the population

Closely related to, and following from the above list is the coupling-strength between nodes, which designates the exact amount of virus transferred between individuals once transmission has been established. Very little information exists on this parameter and indeed it would be onerous to establish. For the purpose of this work the coupling strength (transferred viral load) was chosen as 10% of the concentration of viral load of the node transmitting the virus.

3.2 Simulations

Two experiments of three simulations each were run consecutively to create three comparable populations: a network without controlled nodes, a network with nodes pinned at random and a network with a proportion of the nodes with the highest number of links (sexual partners) pinned. The proportion of nodes pinned was chosen to be 15% of the entire network.

Table 2. Network statistics

Measure	Value	Units
Number of nodes	1000	-
Number of links	3294	-
Average node degree	3.29	-

To obtain comparable populations, it was ensured that the portion of the network governed by stochastic parameters were reset to identical initial conditions between consecutive simulations of non-controlled networks and pinned networks.

For experiment 1, simulations were done over a period of 365 days or 1 year, and for experiment 2 over a period of 5 years.

4. RESULTS

4.1 Experiment 1: 1000 nodes over 1 year

The results from the simulations of three networks, two of which were controlled, are shown in Figure 2 and Table 3. Almost 80% of individuals in the network developed HIV under the randomly-pinned control scheme, while only about 10% developed HIV under the selectively-pinned control scheme.

From the observed Risk Ratios in Table 4, it can be seen that individuals in the randomly-pinned network were 28% less likely to develop HIV over 1 year compared to the uncontrolled network. This number was not statistically significant, given the 95% confidence interval (CI) of $[0.2 - 2.21]$. This confidence interval was calculated using the method described by Giesecke [2002], dividing the Risk Ratio by the error factor in Equation 8 for the lower limit and multiplying by the error factor to obtain the upper limit.

$$e^{1.96\times\sqrt{(1/a+1/b)}} \tag{8}$$

In this equation, a is the risk of HIV for persons in the network of interest (either randomly pinned or selectively pinned). The remaining variable b is the risk of HIV for persons in the uncontrolled network.

It was found that individuals in the selectively-pinned network were approximately 90% less likely to develop HIV over 1 year compared to the uncontrolled network. This result was statistically significant, with a 95% confidence interval (CI) of $[0.074 - 0.132]$.

Table 3. Exposure-Outcome Results for 1000 nodes over 1 year

	HIV+	HIV-	Total
Random Pinning	777	223	1000
Selective Pinning	99	901	1000
No RTIs	850	150	1000

Table 4. Control strategy performance for network with 1000 nodes over 1 year

Measure	None	Random	Selective
Risk Ratio	-	0.78	0.0988
95% CI	-	[0.2-2.21]	[0.074-0.132]

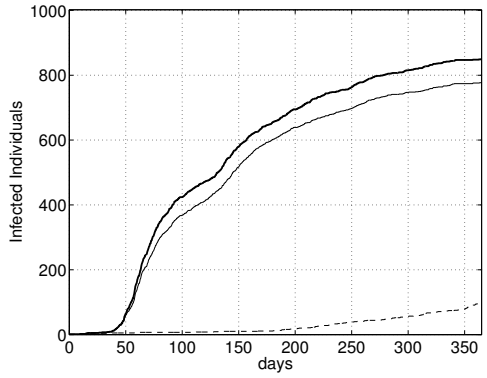

Fig. 2. Experiment 1 for the incidence of HIV for 1000 nodes after using different control schemes over 1 year. Note the difference between the un-controlled network (thick solid), the network pinned at random (thin solid) and the network selectively pinned (dashed).

4.2 Experiment 2: 100 nodes over 5 years

The results from the three networks, are shown in Figure 3 and Table 5. A percentage of 87% of the network developed HIV under the randomly-pinned control scheme, while only 37% developed HIV under the selectively-pinned control scheme over 5 years.

Table 5. Exposure-Outcome Results for 100 nodes over 5 years

	HIV+	HIV-	Total
Random Pinning	87	13	100
Selective Pinning	37	63	100
No RTIs	89	11	100

From the observed Risk Ratios in Table 6, it can be seen that individuals in the randomly-pinned network were 13% less likely to develop HIV over 1 year compared to the uncontrolled network. This number was not statistically significant, given the 95% confidence interval (CI) of $[0.013 - 57.61]$, and most likely caused by the measurement over a small sample size. For individuals in the selectively-pinned network, it can be seen that they were approximately 63% less likely to develop HIV over 5 years compared to the uncontrolled network. This result was statistically significant, with a 95% confidence interval (CI) of $[0.266 - 0.513]$.

Table 6. Control strategy performance for network with 100 nodes over 5 years

Measure	None	Random	Selective
Risk Ratio	-	0.87	0.37
95% CI	-	[0.013-57.61]	[0.266-0.513]

5. DISCUSSION

Given the challenge to assess a human sexual connection network and a control scheme (implying an intervention), a complex-network modelling approach was followed in this work. The nature of real-world data tends to be prone to "self-reporting"-bias, hence estimations of the degree and frequency of connectivity between nodes had to be done or inferred from current literature.

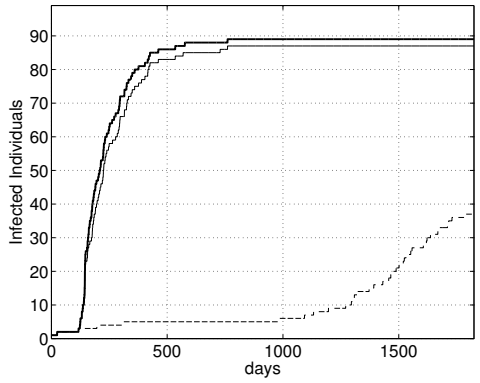

Fig. 3. Experiment 2 for the incidence of HIV after using different control schemes for 100 nodes over 5 years. Un-controlled network (thick solid), Randomly-pinned (thin solid) and Selectively-pinned (dashed).

Several suitable assumptions had to be made to simplify the problem, most notably that all persons in the network are the same, that sexual relations occur continuously, that 1 node starts the infection in a network and that reinfection occurs after first infection. Furthermore, assumptions regarding the varying effect of RTIs, the spread of risk factors in the population and the actual amount of virus transferred between persons were made.

Against this backdrop, and using comparable networks, a clear distinction can be seen between a targeted control approach of selecting people with the most sexual connections and administering RTIs to them, and administering RTIs at random in the population. Even though the average effect of RTIs in the populations may have been overestimated (70% for all individuals), the risk of HIV spread have also been over-estimated by assuming constant daily sexual intercourse between all connections. The simulations thus represent a worst-case scenario of viral spread and very low drug coverage in the population (15%), balanced with a best-case scenario of drug effectiveness.

The main result obtained here was that the two different control strategies rendered vastly different values of HIV incidence in the compared populations. The selective pinning scheme provided a statistically significant result while the random pinning scheme didn't. Of particular interest is the order of reduction in incidence that was seen when the two schemes were compared: In a network with 100 nodes, the incidence in a randomly pinned network was at least twice that of a selectively pinned network. In a network with 1000 nodes, this increased to almost 8 times more. Selective pinning is thus superior in both small and larger networks regarding its effectiveness. It should be noted here that the networks simulated represent sexually connected individuals and not general populations. This explains the high steady-state of infected individuals (Over 85%) seen in the results.

The results obtained in this study are consistent with pinning control scheme results obtained for other unrelated networks of similar structure. Most notably, the conclusion from Wang and Chen [2002] recommended that the most effective arrangement for placing controllers was to choose nodes of the highest degrees.

Other results were also noted as part of the control scheme comparisons. The uptake of HIV increased dramatically much later in the selectively pinned network compared to the randomly pinned network and the uncontrolled network. For the 100-node network, the increased transmission started at 100 days under random pinning and at almost 1000 days (just under 3 years) under selective pinning. This means that selective pinning could delay an HIV epidemic by an order of magnitude if it was possible to implement.

The biggest limitation regarding the practicability of implementing any pinning control scheme is that intimate knowledge about the network structure is needed. If it could be known, the nodes with highest degree should be identified and targeted with suitable additional care.

6. CONCLUSIONS

The challenge with simulating disease networks in the manner presented here lies in affirming the assumptions made regarding sexual behaviour, quantifying viral transfer, establishing the frequency of sexual intercourse and modelling the broad range of risk factors at play in a population. Within the constraints provided by access to suitable data, the model can be refined to include comparisons with known real-world study populations. Disease immune response models can be varied in this architecture to capture a broader range of effects. The co-infection of HIV and TB can also be explored in further work.

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