Biology as Population Dynamics: Heuristics for Transmission Risk

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Abstract

Population-type models, accounting for phenomena such as population lifetimes, mixing patterns, recruitment patterns, genetic evolution and environmental conditions, can be usefully applied to the biology of HIV infection and viral replication. A simple dynamic model can explore the effect of a vaccine-like stimulus on the mortality and infectiousness, which formally looks like fertility, of invading virions; the mortality of freshly infected cells; and the availability of target cells, all of which impact on the probability of infection. Variations on this model could capture the importance of the timing and duration of different key events in viral transmission, and hence be applied to questions of mucosal immunology. The dynamical insights and assumptions of such models are compatible with the continuum of between- and within-individual risks in sexual violence, and may be helpful in making sense of the sparse data available on the association between HIV transmission and sexual violence.

Key Words:
HIV Transmission, Modelling

Introduction

Throughout this special issue, the question of sexual violence is addressed from a number of points of view, and with various methodologies. This article focuses on understanding the biology of sexual transmission (the passage of virions from one person to another) through genital mucosa, and regards overt sexual violence as part of a continuum of risk factors.

We argue that the investigation of transmission risk can benefit from the use of simple models, and from the application of standard modelling techniques such as rescaling of state variables (factors indicating the current state of the system) and parameters (model inputs that capture specific dynamical rules, especially rates, in a quantitative fashion), to identify qualitatively different model behavior, such as having stable or unstable equilibria, or exhibiting a harmful or protective effect of a given stimulus.

A concern which traditionally arises in building models for biological processes is how to capture enough detail to make the model 'realistic', while keeping it simple enough to be formally or computationally tractable, and with few enough parameters that data can be obtained to 'fit' or 'calibrate' the model sensibly. Our approach, which is rather conventional in the applied mathematical analysis of dynamical systems, and is routinely applied within the growing field of biophysics, has not, as far as we are aware, been systematically applied to the problem of HIV transmission – probably partly because movement of infectious material from person to person during intercourse is not a system readily amenable to controlled manipulation and observation. However, even working within the data-poor regime in which this field finds itself, this paradigm has the potential to assist with hypothesis generation and study design: using these tools, many regimes of diverse systems can be summarised into a far smaller number of formally distinct models, the use of which reduces technical difficulty and facilitates the transfer of intuition.

Models of processing around the transmission event itself may be useful to shed light on questions such as

- Are risk factors altered moderately or substantially by sexual violence, relative to consensual sex?
- Are men participating in ongoing sexual violence at particularly high risk of acquisition due to penile trauma, leading in turn to a particularly high risk in the subsequent exposure of women during acute infection of these men?
- What is the plausible range of benefit from topical or systemic post exposure prophylaxis for rape survivors, and over what time scale?
- What specific parameters (such as diffusion length scales, time scales, intermediate event counts, cell densities, etc.) might be measurable in live animal models, explants, or culture experiments, which would correspond to factors impacting the above questions?

To demonstrate these ideas, we outline a simple model which was originally developed to support thinking about HIV vaccines, and then discuss how the model's mathematical form can be reinterpreted in a different context. Parameters can be *modified to accommodate*, while they are *reinterpreted as*, factors other than those originally intended. Beside the focus of this issue on sexual violence, a mature transmission model should shed some light on topical and systemic pre-exposure and post-exposure prophylaxis (PreP/PEP), vaccine development[1], hormonal contraception[2], treatment as prevention (TasP)[3], cervical ectopy[4], differences in viral replication due to the site of infection[5], and the biological impacts of sexual violence on the risk of HIV transmission and acquisition.

Modelling HIV Transmission

Population dynamics-type models[6,7,8] have been widely used to describe systems of cells and virions to assist in understanding viral replication and evolution, and even, in particular, to specific aspects of early infection[9], but, to the authors' knowledge, have not been applied to the process of transmission itself. One interesting finding from studies of early infection is that the pattern of genetic diversity of HIV virus in the weeks after transmission is only consistent, in about three quarters of infections, with the transmission of a single genotype, which has typically been interpreted as the transmission of a single virion[10],. An alternative view is that descendants of other variants may be undetectable because critical early events, or relatively minor differences in replicative fitness, accumulate exponentially over viral life cycles to produce a strong dominance by the descendants of one of several founder variants. Nevertheless, it is biologically plausible to model transmission risk as the likelihood of establishing a single founder strain, which facilitates simplifications of the models relative to a more general case where there are many possible pathways to infection, involving a wide range of possible numbers of transmitted virions.

Starting from this view, a population dynamics-type model[11,12] was previously developed by Welte and Walwyn[13] in order to capture the initial exposure of susceptible immune system cells to HIV virions. Whether or not an exposure develops into systemic infection is determined by random events within a lifecycle model which includes background and immune system-mediated hazards for invading free virions, cell invasion leading to a first generation of infected cells, and cell-to-cell transmission of virions. The initial design of this model attempted to capture the following important characteristics of infection:

- The probability of transmission (male to female) is low[14,15] and approximately proportional to viral exposure dose and endocervical susceptible lymphocytes.
- Successful transmission is mostly due to the survival of a single genotype[16], suggesting that there is significant screening of the initial HIV in semen dose and that only a very small number of wild-type virions break through the immune barrier(s).
- Higher rates of transmission are found in the presence of genital tract inflammation and other sexually transmitted diseases[17,18].
- The epithelial layer can be considered as an initial 'barrier zone'[19]. Generally this barrier zone is effective, but once breached, the infection spreads to local T cells and macrophages, and also the interstitial dendritic cells, following which the infection spreads rapidly as a result of the formation of dendritic/T cell clusters which migrate into the regional lymph nodes.
- The probability of transmission has been seen to increase in early vaccine trials[20,21].

We consider the development of appropriate population-dynamic models of initial infection to be a long term process, requiring new inputs and insights into the very early stages of infection[22]. For the purpose of exploration, we developed a simplistic model based on the following:

- We assume that the susceptible individual is challenged by a number of free virions, such as an HIV-positive male exposing a sexual partner to HIV-bearing semen.
- The invading virions are characterised by a mortality μ (probability per unit time of irreversible virion disintegration) and a 'fertility' f (probability per unit time of infecting a cell).
- Any infected cells produced by invading virions are subject to a mortality λ (probability per unit time of irreversible cell disintegration).
- For a characteristic time T, first-generation infected cells, assumed to be superficially located by virtue of having encountered free virus, have negligible prospects of spawning virions in

sufficient proximity to *other* susceptible cells for there to be a chance of generating second-generation infected cells.
- A first-generation infected cell which survives for a time T has a high chance of reaching a locus of more susceptible cells, leading thereafter to the rapid establishment of a systemic infection.

Using standard survival analysis, we explore this model when all rates are presumed to be constant, although in principle, all of μ , λ and f are potentially functions of time. Survival to time T is given by

$$S(T) = S = e^{-\lambda T}$$

The probability of a single virion successfully infecting a cell is given by its expected net fertility

$$F = \frac{f}{f + \mu}$$

which just expresses cell invasion as a fraction of the total environmental opportunity and hazard, where $\mu = \mu b + \mu i$, the baseline and immune-induced mortalities. Any first-generation infected cell has a probability of survival for a time T, and the probability that a single invading virion leads to an infected second-generation cell after time T is then given by

$$P = FS = \frac{f}{f+\mu}\, e^{-\lambda T} \ll 1.$$

We now demonstrate the qualitative application of our ultimately very formal quantitative model with the intention of exploring generic questions such as:

- Does the system behave in qualitatively different ways for different ranges of parameter values?
- Are there interesting trade-offs between forces or factors, or is there synergy?
- Are superficially separate factors really distinguishable, and do they require independent assessment and measurement, or do they ultimately manifest only in combinations which can be observed through their net/combined effect?
- Can an analysis of the model outputs help to build intuition and formulate concrete hypotheses which feed into experimental designs?

Returning to our demonstration model, the probability that an exposure becomes an established infection depends explicitly on four *parameters* which capture the hypothetical dynamical rules: μ, λ, T and f. It is unlikely that these can each be reliably measured at present, so we consider a slightly abstract approach. A perturbation of the system, such as the administration of a vaccine designed to elicit a neutralising antibody response, was initially of interest. While it is impossible to predict how a vaccine might affect each parameter of the system, it is common, across very wide categories of models, for small perturbations to dynamical systems to have at least an initial regime where most parameters respond linearly to the perturbation, especially if the perturbation does not cause very fundamental changes in the system. If one has knowledge of the dynamics, this simple impact on the parameters (i.e. the rules) can be translated, using mathematical techniques, into the much harder-to-guess, -intuit, or -observe, impact on the system state.

Given these simplifying assumptions, we can use standard modelling methods to construct all possible 'intrinsic' parameters of the system, noting in particular the dimensionless parameters, i.e. those without arbitrary units for such quantities as time, size, etc. Because the size of these dimensionless parameters (which are often ratios of parameters of the same units/dimension) are independent of the practical choice of measurement units, they can be used to provide 'intrinsic' criteria, which determine the qualitative regimes of the system. Importantly, this allows us to state in a logically consistent manner whether effects are *small* or *large*, synergistic or antagonistic. As illustrated in the original vaccine application, an antibody vaccine affects the system in the following ways:

- It increases the probability of incoming virions being neutralised, thereby increasing μ
- It leads to general immune system activation, hence increasing the density of available target cells[23], or an increase in f.

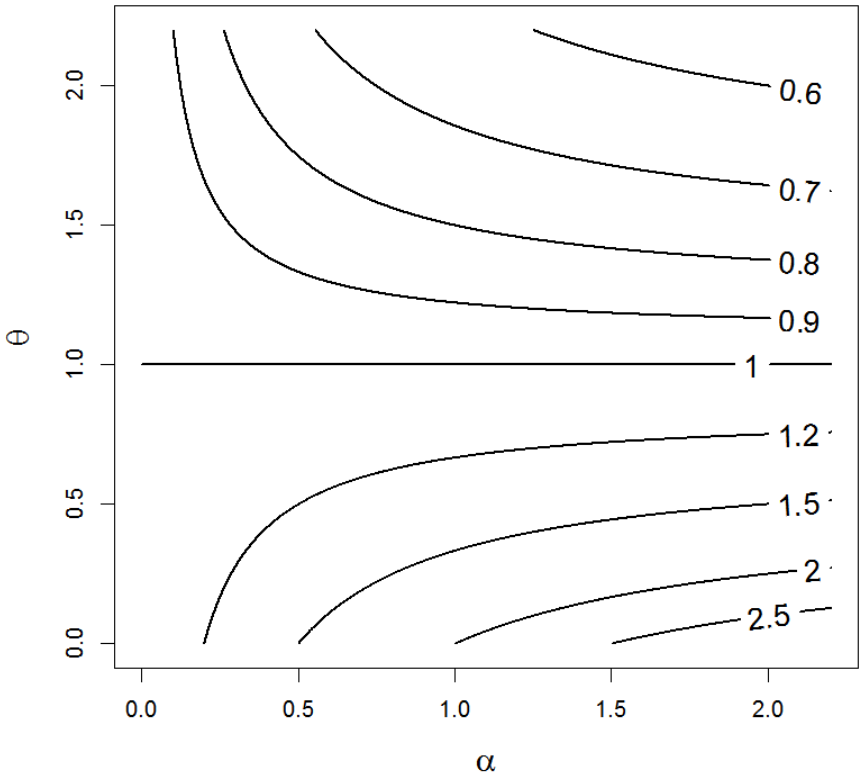

Fig. 1. Risk of infection after stimulation by a "neutralizing antibody vaccine" of strength α, relative to risk of infection before stimulation, given the relative efficiency Θ of a specific vs. general immune system response.

Without providing any particular numerical values for individual underlying parameters, it can be formally shown (as demonstrated numerically in Figure 1) that the effect of the vaccine is beneficial, or deleterious, depending on whether the ratio of the 'relative' efficiency of these two effects is greater, or less than, one, respectively, as captured by the "universal response parameter" Θ:

$$\theta = \frac{f_0 \mu'}{f' \mu_0} = \frac{\frac{\mu'}{\mu_0}}{\frac{f'}{f_0}}$$

where the primed symbols are the rates of change of the parameters with respect to imposition of the perturbation. Formally, this is derived by Taylor-expanding the probability of transmission, in the case of a perturbation, around the value in the absence of a perturbation, and taking the ratio of the perturbed and unperturbed values. Importantly, because the density of susceptible cells is directly proportional to the parameter f, but the density of neutralizing antibodies is proportional only to a portion, μ_i, of μ, it is likely that $\theta < 1$, i.e. that the probability of infection will be increased by an immune response which increases the density of a broad range of immune cells, all susceptible to infection and of which only a portion act as neutralizing agents.. This formal relationship suggests direct measurements of changes in μ and f, which might be measurable in-vitro, or in non-human primate models.

A CTL-stimulating vaccine can be defined as one which

- Increases the mortality (λ) of the first generation of infected cells
- Generally activates the immune system, as in the case of the antibody vaccine, hence increasing the parameter f.

Now it can be shown that the relative risk of transmission, as a function of the strength α of the vaccine stimulus, and a more complex notion of relative efficiency Γ is given (see Fig. 2) by

$$R(\alpha) = \frac{1+\alpha}{1+\theta\alpha} e^{-\Gamma\alpha}$$

where

$$\Gamma = \frac{f_0 T \lambda'}{f'}$$

This shows quite different, and more complex behaviour, in that, under the model assumptions, a suitably 'strong' stimulus will always be protective, but that depending on the parameter Γ, which captures the trade-off of the various components of immune system stimulus, the perturbation may need to be 'sufficiently large'. This is the result of non-linearity in the way the various parameters enter the dynamics.

Variations on this theme of the vaccine stimulus can be considered. For example:

- The transit time T within which a primary infected cell needs to encounter further target cells would be shortened by mucosal trauma or inflammation[24,25], which in turn could be studied in relation to mechanical or chemical stresses.
- Stress, nutrition, and general (as opposed to genital) trauma could be linked to systemic immune activation or suppression, leading to changes in f (perhaps in either direction).

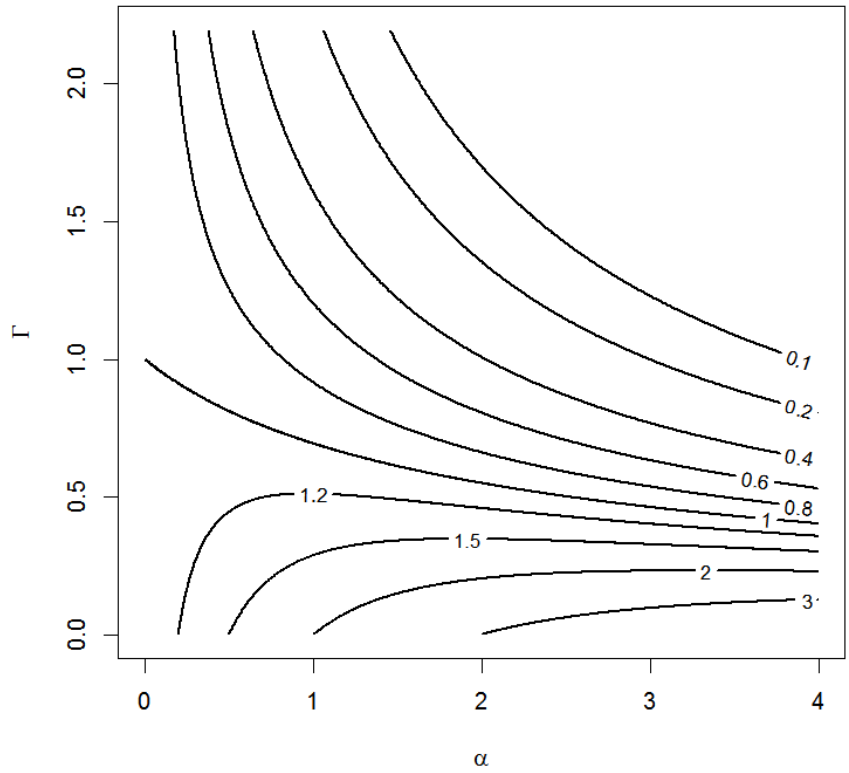

Fig. 2. Risk of infection after stimulation by a "CTL vaccine" of strength α, relative to risk of infection before stimulation, given the relative efficiency Γ of a specific vs. general immune system response.

- Correlation to acute infection, such as in serial violent encounters involving disproportional risk of recent acquisition by men, may lead to 'recently transmitted' virus, selected for larger values of f (more efficient cell entry), or smaller values of μ (greater structural stability, or evasion of neutralising agents).

As noted earlier, an initial assumption of this model is that transmission risk is proportional to viral dose. More recent work has shown that this risk appears to scale non-linearly with viral load[26,27]. At levels below 100,000 RNA copies per ml, the risk of transmission can be predicted using a power law between the two variables (i.e. a linear correlation based on the logarithmically transformed data). However at higher viral loads, further increases in RNA copies per ml are not associated with a greater risk of transmission[28,29,30]. It has been pointed out that it is more biologically plausible, and a good fit to the data, to view this as a linear increase for smaller viral loads, and a saturation for higher viral loads.

This interpretation is consistent with the view that sexual contacts at low viral loads carry minimal risk, but extra viral load does indeed increase risk in direct proportion to viral load up to the saturation point, beyond which this effect is insignificant relative to other factors. The latter may include saturation kinetics of T cell responses and the dynamics of macrophage recruitment. It was noted previously that counting transmitted virions is not straightforward, so that it is unclear whether multiple transmissions are as uncommon as they superficially seem (about a quarter of

cases). This aspect warrants further investigation, and in particular whether, and which, microscopic factors sensitively affect acquisition risk. It is plausible, and disconcerting, that violence-associated risk factors may be a substantial contributor to the risk of infection, if not epidemiologically, then potentially still at the level of the individual.

Conclusion

Our purpose in this article is to outline the utility of a simple statistical model in identifying important dynamical regimes, as defined by a set of broadly conceptualised mathematical parameters, and hence developing relevant experimental hypotheses.

Model equations cannot distinguish between any external factors which have the same effect on the model parameters. Hence, a pre-exposure prophylaxis regimen which inhibits reverse transcription could also be seen as reducing viral 'fertility' f; and other active ingredients, or pharmacological actions, could induce changes (perhaps in either direction) in general inflammation of, or immune cell trafficking to, the mucosal interface (collectively influencing the parameter λ). Emotional and physical trauma associated with violence could also affect immunity to infectious diseases, but the relationship between stress and the immune system is complex: for instance, although chronic stress has a negative impact on immune function, short-term stress may boost immune activity, including natural-killer-cell activity and leukocyte release[31].

Traditionally, modelling is dichotomised into 'deterministic' and 'stochastic' (probabilistic / statistical) rules. The former tend to capture abstract 'rules', and also the emergent or average behaviour of systems of sufficient size. In work on HIV transmission, mature probabilistic models are mainly the ones used for conventional 'data analysis' such as estimation of associations between 'risk-factors' and 'outcome'. The crucial processes of transmission, at the individual level, are highly variable and unpredictable. Modelling and unpacking these processes explicitly will involve hybrid models which have proven difficult to construct, mainly due to a lack of detailed data to assist in model selection. We argue that these difficulties can be addressed, in part, by using immature models to generate hypotheses about early post-exposure events and the variability and correlates of risk, and to sharpen experimental designs and analyses through the improved characterisation of intrinsic system behaviors.

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