International Conference and Advanced Workshop on Modelling and Simulation of Complex System (ICAWMSCS)

Seminar Series I

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SENSITIVITY ANALYSIS OF A HIV SUPERINFECTION MODEL

Presenter

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OUTLINE

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▶ Interpreting the numerical values of the sensitive parameters

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HIV/AIDS

- Acquired Immune Deficiency Syndrome (AIDS), an infectious disease caused by the invasion of Human Immunodeficiency Virus (HIV) (Assefa and Gilks, 2020).

- HIV binds itself to its target cells, CD4 T-cells (Ahmad, Khan, Akbar, & Al-Moneef, 2023), hijacks the system and proliferate itself within the cells.

- It gradually destroys the ability of the immune system to fight against other infections and diseases such as Tuberculosis, Hepatitis B, Hepatitis C and Cancer (National Institutes of Health, 2023).

- A blood count of CD4 T-cells less than $200\ cells/mm^3$ shows that HIV has engulfed the system. Disease has progressed to AIDS stage (WHO, 2007).

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Global impact of HIV/AIDS

- Though there are notable efforts in the fight against HIV, this viral infection has continued to spread AIDS globally

- AIDS has not only affected the health of humans, it has also had severe impact on household, communities, economic growth and the world at large (Barré-Sinoussi, 1996; Gallo & Montagnier, 2003).

- The first case was reported in 1981 in the United States, since then, not less than 40 million deaths have been reported, with about 84 million infection globally (Payagala & Pozniak, 2024).

- The low- and middle-income countries accounts for about 58% of the people with HIV, basically among people living in southern and eastern Africa. The western and central Africa share 13%, 15% in the Pacific and Asia, while the Western and Central Europe and North America takes 5% (Payagala & Pozniak, 2024).

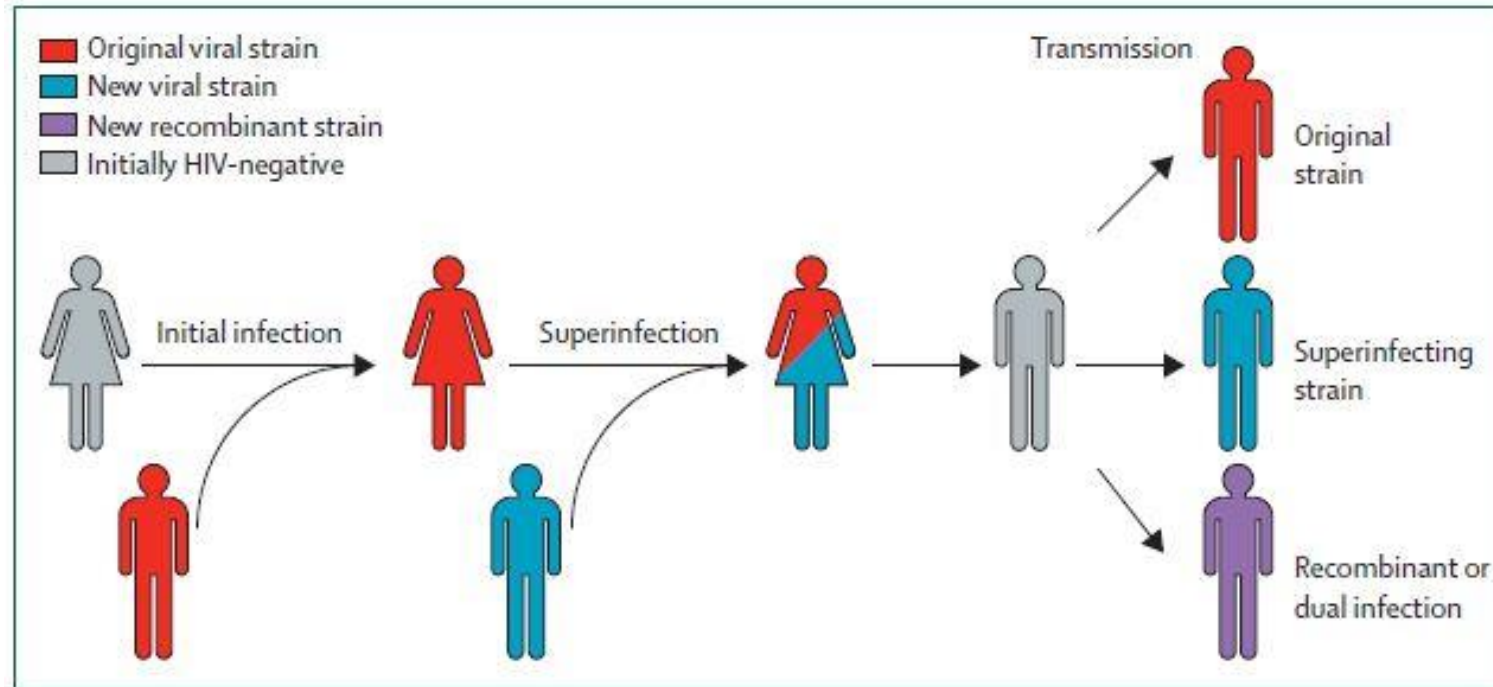*Presenter:*

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HIV Superinfection

- HIV Superinfection is the reinfection of an already infected person with a unique strain of HIV after the establishment of the primary infection (Sun and Xiao, 2016).

- HIV has two types: HIV-1 and HIV-2.

- The first case of HIV superinfection was reported in 1987 (Smith, Richman & Little, 2005). Incidence rates for HIV superinfection has been reported to lie between 0% and 7.7% annually.

- The new strain can replace the original strain or co-exist with the original strain or in some cases recombine to form another generation of viral strain .

- Superinfection may cause some people to get sicker faster because the new strain of the virus could be resistant to therapy. Early treatment with Highly Antiretroviral Therapy could however help to hinder progression to superinfection (Blackard, Cohen & Mayer, 2002; Moreh, Szilagyi, & Scheuring, 2018).

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HIV Superinfection

Source: *Lancet Infect Dis* 2013; Vol. 3: pp. 622-28

Figure 1: HIV Superinfection Transmission Pattern

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HIV Superinfection Model

$$\frac{dU(t)}{dt} = s - \beta V_p(t)U(t) - \mu U(t) \tag{1}$$

$$\frac{dI_p(t)}{dt} = \beta V_p(t)U(t) - \alpha V_s(t)I_p(t) - \mu I_p(t) \tag{2}$$

$$\frac{dI_s(t)}{dt} = \alpha V_s(t)I_p(t) - \mu I_s(t) \tag{3}$$

$$\frac{dV_p(t)}{dt} = \rho N_p I_p(t) + (1 - \gamma)N_s I_s(t) - \beta V_p(t)U(t) - \delta V_p(t) \tag{4}$$

$$\frac{dV_s(t)}{dt} = \gamma N_s I_s(t) - \alpha V_s(t)I_p(t) - \delta V_s(t) \tag{5}$$

Equations (1) – (5) are subject to the following inequalities initial conditions:
$U(0) > 0$, $I_p(0) \geq 0$, $I_s(0) \geq 0$, $V_p(0) \geq 0$ and $V_s(0) \geq 0$, where $s = \pi + \Lambda$.

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Basic Reproduction Number (R_0)

- In disease modelling, thresholds such as R_0 depend on the parameters of the differential equation model.

- The parameters are estimated from the fittings (or from available data information), and are used to compute the threshold.

- Epidemiologists are usually concerned with the ability of the disease to spread in a system. Basic reproduction number provides a degree of the ability of a disease to infect and spread in a population (Van de Driessche & Watmough, 2002).

- R_0 is the number of post-primary occurrence that HIV superinfection will result into in the population of healthy CD4 T cells that has no immunity to HIV and at the same time, has no strategy to control the infection.

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Basic Reproduction Number (R_0)

$$J(E) = \begin{pmatrix} -\mu & 0 & 0 & -\frac{\beta s}{\mu} & 0 \\ 0 & -\mu & 0 & \frac{\beta s}{\mu} & 0 \\ 0 & 0 & -\mu & 0 & 0 \\ 0 & \rho N_p & k_1 & k_2 & 0 \\ 0 & 0 & \mu N_s & 0 & \delta \end{pmatrix}$$

(6)

where $k_1 = (1-\gamma)N_s$ and $-\left(\frac{\beta s}{\mu} + \delta\right)$. R_0 is the largest eigenvalue of the Jacobian matrix in equation (21). R_0 was obtained using the Jacobian stability approach (Martcheva, 2015). It is given as

$$R_0 = \sqrt{\frac{\beta(\pi+\Lambda)N_p}{\beta(\pi+\Lambda)+\mu\delta}}$$

(7)

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Why Sensitivity Analysis

- When we vary model parameters, the output of the model changes.

- The goal of sensitivity analysis is to decide which parameters of the model are most influential in the model output (Wachira, Lawi & Omondi, 2022).

- Sensitivity Analysis can be carried out on a dynamical system such as the reproduction number.

- A parameter is said to be sensitive if small changes in its value results into large changes in the solution of the differential equations.

- We could carry out a local sensitivity analysis and global sensitivity analysis.

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Methods for sensitivity test

- There are several methods for testing the sensitivity of parameters of a model. Wu, Dhingra, Gambhir and Remais (2013), enumerated some of these methods to include the

  ❑ Partial Rank Correlation Coefficient (PRCC),

  ❑ Latin Hypercube Sampling (LHS),

  ❑ Normalised Forward Sensitivity Index (NFSI),

  ❑ Regression Analysis,

  ❑ One-Way Sensitivity Analysis, and

  ❑ Sobol Method and Sensitivity Heat Map Method.

- In this presentation, the normalized forward sensitivity indices, as discussed by Diekmann, Heesterbeek and Metz (1990), was used to determine sensitive parameters in reproduction number (R_0).

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The Normalized Forward Sensitivity Index (NFSI)

$$X_y^{R_0} = \frac{\partial R_0}{\partial y} \times \frac{y}{R_0} \qquad (8)$$

y Is the parameter of interest.

$$X_\beta^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} \qquad (9)$$

$$X_{N_p}^{R_0} = \frac{\partial R_0}{\partial N_p} \times \frac{N_p}{R_0} \qquad (10)$$

$$X_\pi^{R_0} = \frac{\partial R_0}{\partial \pi} \times \frac{\pi}{R_0} \qquad (11)$$

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Parameter values used for estimation

Table 1: Parameter Values

Parameters	Values	Sources
β	$0.000024 \text{mm}^3\text{day}^{-1}$	Ngina (2018)
N_p	100day^{-1}	Mbogo et al., (2018)
π	100mm^{-3}	Ngina (2018)
Λ	0.03day^{-1}	Roy and Chartterjee (2010)
μ	0.02day^{-1}	Roy and Chartterjee (2010)
δ	0.02day^{-1}	Culshaw and Ruan (2000)

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Result of Sensitivity Analysis

Table 2: Results of Numerical Sensitivity of Parameters in R_0

Parameters	Values
β	+04483
N_p	+0.0161
π	-0.0001

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Interpretation of values of the sensitive parameters

- From the results of sensitivity analysis presented in Table 2, it can be seen that β (the rate of infection of viral strain 1) is the most sensitive parameter of the model.

- This shows that the rate of infection of the primary strain has the greatest effect in the system.

- In a nutshell, increasing β will imply increase in the rate at which cells are primarily-infected. This will result in a higher value of R_0.

- The converse is true. By epidemiological interpretation, a larger value of R_0 implies that the system will become endemic. It is observed that the population of virions in the system is on a sharp increase.

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Interpretation of values of the sensitive parameters

- The parameter, N_p, which is the amount of viral strain 1 produced upon successful lysing of infected CD4 T cells is also positive.

- Infection rate of the first viral strain is higher than of the second This agrees with the clinical findings of Vidya Vijayan (2017).

- The source term, π, for the production of uninfected cells triggered by the invasion of viral strain 1 is negative. This reveals that π does not contribute to the endemicity of the system as it will reduce the value of R_0. Thus, the population of new uninfected CD4 T cells that are produced as infection triggers the system has no significant effect in combating viruses in the system.

- Sensitivity Analysis was not carried out on naturally occurring parameters. We assume that their values are independent of the activities of the viral strains in the system.

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