Immuno-epidemiological Model for Transient Immune Protection

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Background & Motivation

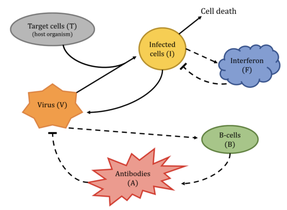
Infectious diseases pose a significant public health threat, necessitating comprehensive understanding of their transmission dynamics. Previous research in mathematical biology has focused on the immune response dynamics within naive hosts. However, a research gap persists around the impact of re-exposure during ongoing outbreaks on immune responses of previously infected individuals.

Our study addresses this gap by investigating a modified differential equations model with re-exposure events, called a flow-kick system. We aim to analyze the behavior of the flow-kick system under stochastic perturbation, where re-exposure events occur randomly according to various probability distributions.

The incorporation of stochasticity in the flow-kick system allows for a more realistic representation of real-world outbreak dynamics. Findings from this research may contribute to the development of improved models and strategies for infectious disease control and prevention.

Model

- Our influenza model integrates innate and adaptive immunity, including virus (V), target cells (T), infected cells (I), interferon (F), B-cells (B), and antibodies (A). We examine the virus's impact on target cells, generating more infected cells and virus. Innate immunity eliminates infected cells through interferon (F), while adaptive immunity employs B-cells (B) producing antibodies (A) to neutralize the virus.



- The variables V, T, I, F, B, A represent quantities of the immune system components described above. The interactions between these components are modeled according to the following system of differential equations.

$$\begin{aligned}
\dot{V} &= pI - cVA - \mu VA - \beta VT\tfrac{V}{V_m+V} \\
\dot{T} &= gT\left(1 - \tfrac{T+I}{C_t}\right) - \beta' VT\tfrac{V}{V_m+V} \\
\dot{I} &= \beta' VT\tfrac{V}{V_m+V} - I - \kappa IF \\
\dot{F} &= qI - dF \\
\dot{B} &= m_1 V(1-B) - m_2 B \\
\dot{A} &= m_3 B - rA - \mu' VA
\end{aligned}$$

- A deterministic flow-kick model takes a solution of the system of differential equations described above and introduces instantaneous perturbations of size k of the solution at discrete times with inter-kick time τ.
- A stochastic flow-kick model uses random values for k and τ.
- k denotes sudden exposure events (modeled by discrete increases in virus).
- flow time τ represents the inter-kick time.
- An excursion (observable illness) is defined as a scenario where the number of infected cells exceeds a threshold (2.5×10^5) after a short burn-in period (5 days) since the simulation's initiation.
- We employ a Monte Carlo simulation of the stochastic flow-kick system. Kicks are sampled uniformly from a given interval, and flow times are sampled either uniformly or through a Poisson process.

Objectives

- Simulate the probability of reinfection and the time to reinfection when kick size k is uniformly distributed on a fixed range and flow time τ is uniformly distributed or exponentially distributed.
- Quantify the relationship between the probability of infection and time to reinfection with respect to the parameters of the distributions of k and τ.

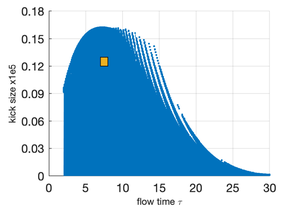


Figure 1. [3] Safe zone with respect to k and τ

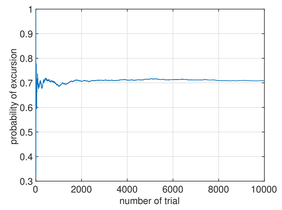


Figure 2. Probability of infection vs. number of trails

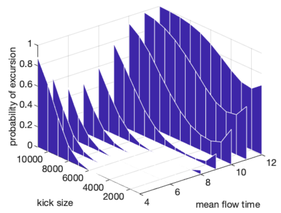


Figure 3. Probability of reinfection

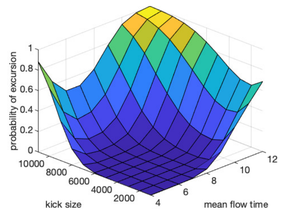


Figure 4. Smooth interpolation of slices in Figure 3

Results: uniformly distributed τ

Figure 1 [3]: The blue region in the Figure 1 represents values of k and τ for which an excursion does not happen in the deterministic flow-kick system. We call this the safe zone.

Figure 2: In the stochastic flow-kick system, whether an excursion happens for given values of k and τ is uncertain. If k and τ are uniformly sampled from the yellow rectangle depicted in Figure 1, the probability of excursion is approximately 71%. Figure 2 shows convergence to this value using Monte Carlo simulation. Not shown in the figure is the fact that the mean time to excursion is approximately 408 days.

Figure 3: The yellow rectangle in Figure 1 represents values of k and τ where $12000 < k < 13000$ and $7 < \tau < 8$. We wish to approximate the probability of excursion given that we sample k and τ uniformly over other subregions of the blue safe zone of Figure 1. We sample uniformly over subregions of the form $k_0 < k < k_0 + 1000$ and $\tau_0 < \tau < \tau_0 + 1$. Figure 3 shows the dependence of the probability of excursion (z-axis) on the values of k_0 and τ_0 for $k_0 = 1000, 2000, ..., 11000$ and $\tau_0 = 4, 5, ..., 12$. Figure 4 shows a smooth interpolation of the slices depicted in Figure 3.

Figure 5: For τ_0 small enough, the relationship between probability of excursion and k_0 is approximately logistic, smoothly increasing as k_0 increases. A logistic regression fit is depicted in Figure 5. Such fits might be possible for other values of τ_0 if the range of k_0 is restricted appropriately. Note that the $\tau_0 = 7$ slice of Figure 3 is graphed using a portion of the data used in Figure 5.

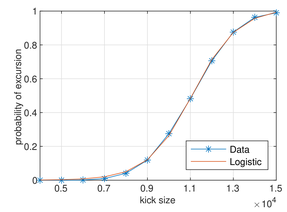


Figure 5. Probability of infection vs. k_0, when $\tau_0 = 7$

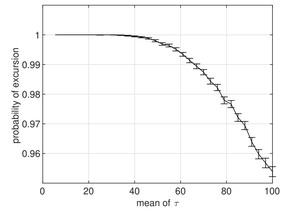


Figure 6. Probability of infection vs. mean of τ

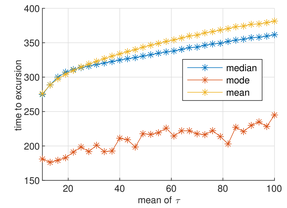


Figure 7. Mean/median/mode of time to reinfection

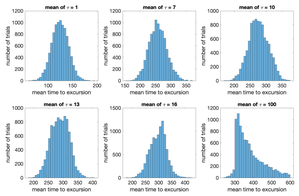


Figure 8. Histogram of the time to excursion

Results: exponentially distributed τ

We conducted 60000 simulations to analyze the stochastic flow-kick system, sampling τ from exponential distribution with its mean varying from 7 to 100, while sampling the kick size k uniformly between 12000 and 13000.

Figure 6: The data elucidates a noteworthy correlation: when the mean flow time remains under 40 days, individuals experience an almost certain probability (close to 1) of reinfection. As the mean flow time increases, the probability of reinfection exhibits a corresponding downward trend.

Figure 7: The yellow, blue, and red curves respectively represent the relationship between the mean, median, and mode of the time to reinfection with the mean flow time. As the mean flow time increases, these three curves display a synchronous upward trend. This pattern implies that extended intervals between exposures are associated with a longer timespan required for an individual to encounter reinfection.

Figure 8: The presented histograms illustrate various distributions of time to excursion, each corresponding to a distinct mean flow time. When the mean of τ is 1, the time to excursion appears to be a normal distribution. However, as the mean of τ increases, the distribution becomes progressively more right-skewed.

Future directions

- Validate the hypothesis that as the mean flow time increases, the time to excursion tends to follow a normal distribution.
- Establish a quantitative relationship between the distribution of τ and the distribution of the time to excursion.

References

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