Immuno-epidemiological Model for Transient Immune Protection

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Background

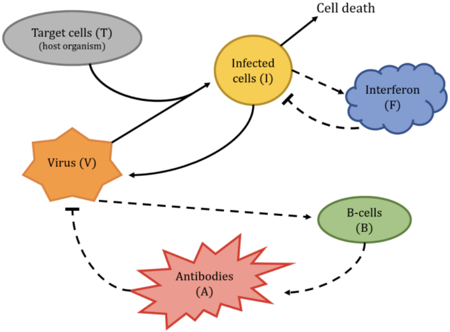
- We will focus on the flow-kick system, which is a modification of the differential-equations model that introduces kicks at predetermined times.
- Known: the behavior of the system in the context of immune system modeling with **deterministic** kick magnitudes and times.
- Goal: explore the behavior of flow-kick systems when kick magnitudes and times are random and chosen according to probability distributions.

Main Questions

1. Add randomness: What happens when the exposure size and timing vary?
2. Uniform sampling vs. Exponential sampling: What happens when we use different probabilistic sampling methods?
3. How does the value of λ (the average number of kicks within a certain time interval) influence the reinfection rate?

Influenza model: innate immunity and adaptive immunity

- The virus(V), target cells(T), and infected cells(I) make up a subsystem where the virus infects the target cells to produce more infected cells and more virus.
- The interferon(F) represents the innate immune function and kills infected cells, while the adaptive immunity includes B-cells(B) that produce antibodies(A) that neutralize the virus.



System of Differential Equations

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

Figure: differential equations

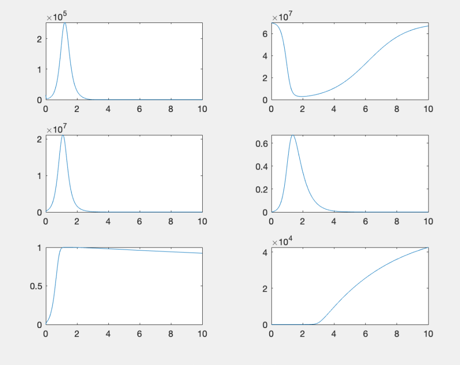
Par	Description	value	units
p	viral production rate	0.35	$u_V/(u_T d)$
c	viral clearance rate	20	$1/d$
μ	rate of viral loss per unit of antibodies	0.2	$1/(u_A d)$
μ'	rate of antibody loss per virion	0.04	$1/(u_V d)$
β	rate of viral loss per target cell	5×10^{-7}	$1/(u_T d)$
β'	rate of conversion from target cells to infected cells per virion	2×10^{-5}	$1/(u_V d)$
V_m	half-activation for viral growth	10	u_V
g	basal growth rate of healthy target cells	0.8	$1/d$
C_t	maximum cell capacity of the target tissue	7×10^{7}	u_T
δ	death/removal rate of infected cells	3	$1/d$
κ	killing rate of infected cells per unit of interferon	3	$1/(u_F d)$
q	interferon production rate	1×10^{-7}	$u_F/(u_T d)$
d	interferon degradation rate	2	$1/d$
m_1	rate of B-cell activation per virion	1×10^{-4}	$1/(u_V d)$
m_2	rate of B-cell deactivation	0.01	$1/d$
m_3	antibody production rate from B-cells	12000	u_A/d
r	antibody degradation rate	0.2	$1/d$
k	kick size representing viral exposure	order 10^4	u_V

Figure: parameters

Six-plots with Initial Condition

1. Initial Condition:

$$\begin{bmatrix} V \\ T \\ I \\ F \\ B \\ A \end{bmatrix} = \begin{bmatrix} 15000 \\ 7 \times 10^7 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$



$\tau \sim \text{Unif}(7,8)$

- k represents re-exposure dose magnitude: $12000 < k < 13000$
- τ represents inter-exposure interval, i.e. time between kicks: $7 < \tau < 8$
- Out of 500 simulations, 386 (77)%) of the simulations had an excursion when t=600.

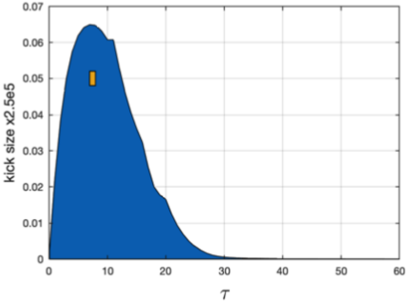


Figure: τ vs. k

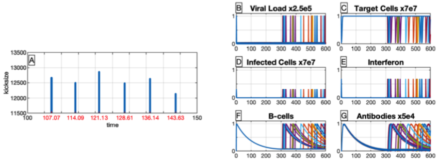


Figure: stochastic simulation (Alanna)

$\tau \sim \text{Unif}(7,8)$

Add randomness:

- $a = 0$
- $b = 1000$
- $k = [12000 + (a + (b - a) * rand]$
- $\tau = 7 + 1 * rand(85, 1)$

```
IC = [15000; 7*10^7; 0; 0; 0; 0];
k_V = 0;
k = [k_V 0 0 0 0 0];
tau = 7+1*rand(85,1);
steps = find(cumsum(tau) >= 600,1)-1;
tau = tau(1:steps);
a = 0;
b = 1000;
tall = [];
Yall = [];
kall = [];

for c = 1:steps
    [ts, Ys] = ode45(f,[0,tau(c)], IC);
    k = [12000 + (a+(b-a)*rand), 0, 0, 0, 0, 0];
    IC = Ys(end,:) + k;
    tall = [tall; ts+sum(tau(1:(c-1)))];
    Yall = [Yall; Ys];
    kall = [kall; k(1)];
    %excursioncheck(tall, Yall);
end
```

$\tau \sim \text{Unif}(7,8)$

Strong law of large numbers: Let $X_1, X_2, \ldots$ be an i.i.d sequence of random variables with finite mean μ, $X_i \sim Ber(p)$. Let $S_n = X_1 + \cdots + X_n$. Then as $n \to \infty$,

$$P(\lim_{n\to\infty} \frac{S_n}{n} = \mu) = 1,$$

which implies that

$$\lim_{n\to\infty} \frac{X_1 + \ldots + X_n}{n} = E[X] = p = \mu.$$

$\tau \sim \mathrm{Unif}(7,8)$

The Central Limit Theorem: Let $X_1, X_2, \ldots$ be an i.i.d sequence of random variables with finite mean μ and variance σ^2. For $n = 1, 2, \ldots$, let $S_n = X_1 + \cdots + X_n$. Then as $n \to \infty$,

$$\frac{S_n/n - \mu}{\sigma/\sqrt{n}} \sim \mathcal{N}(0,1),$$

$$\frac{S_n}{n} - \mu \sim \frac{\sigma}{\sqrt{n}}\mathcal{N}(0,1),$$

$$\frac{S_n}{n} \sim \frac{\sigma}{\sqrt{n}}\mathcal{N}(0,1) + \mu,$$

$$\frac{S_n}{n} \sim \mathcal{N}(\mu, \frac{\sigma^2}{n}),$$

which implies that as $n \to \infty$,

$$p = \frac{S_n}{n} \sim \mathcal{N}(\mu, \frac{\sigma^2}{n}).$$

$\tau \sim \text{Unif}(7,8)$

Excursion Check Function

- Excursion: in the positions minimum time to the end, check if $Y_s \geq 2.5 \times 10^5$.
- Outputs: excursion result (0's and 1's), excursion time (quantitative)
- mean time to excursion = mean(excursion time)
- probability of excursion = mean(excursion result)

```
if max(Ys(minimum_time:end,1)) >= 2.5*10^5
    %max of virsus in positions minimum_time to end, checking if that is >=2*10^5
    %display('excursion')
    index_of_excursion = find(Ys(minimum_time:end,1) >= 2.5*10^5,1)+minimum_time;
    Ys(index_of_excursion,1);
    ts(index_of_excursion);
    output = 1;
    output2 = ts(index_of_excursion);
else
    output = 0;
    output2 = NaN;
    %display ('no excursion')
end
```

$\tau \sim \text{Unif}(7,8)$

Probability of excursion

- $n = 10000$
- Probability of excursion ≈ 0.7090
- Mean time to excursion ≈ 408.7978

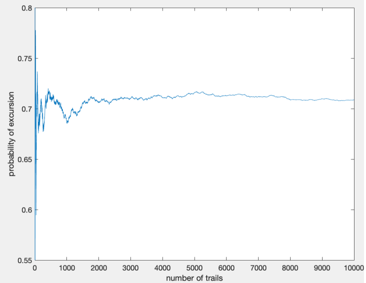


Figure: probability of excursion vs. number of trails

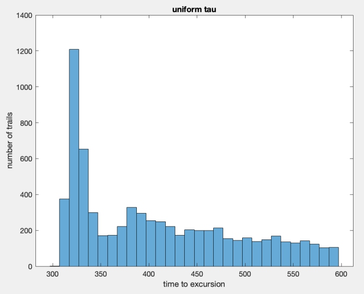


Figure: histogram of time to excursion

$\tau \sim \mathrm{Unif}(7,8)$

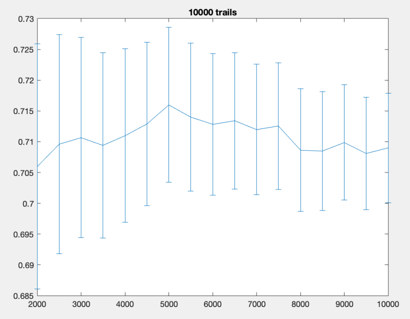
Construct Confidence Interval

- According to the Central Limit Theorem,

$$p = \frac{S_n}{n} \sim \mathcal{N}(\mu, \frac{\sigma^2}{n}),$$

we construct the Confidence Interval,

$$CI = [y \pm \frac{\sigma}{\sqrt{n}} \times 1.96], \text{ where } \sigma = 0.4542,\ 2000 \leq n \leq 10000$$



$N \sim \mathrm{Pois}(\lambda),\ \tau \sim \mathrm{Exp}(\frac{\lambda}{600})$

- k represents re-exposure dose magnitude: $12000 < k < 13000$.
- N represents the number of kicks over time interval $[0, 600]$: $N \sim \mathrm{Pois}(\lambda)$, i.e. $N \sim \mathrm{Pois}(\frac{600}{7})$.
- U represents the exact times when kicks happen: $U \sim \mathrm{Unif}(0, 600)$
- τ represents time between kicks: $\tau_n = U_n - U_{n-1}$. $\tau \sim \mathrm{Exp}(\frac{\lambda}{600})$, $E[\tau] = \frac{600}{\lambda}$, i.e. $\tau \sim \mathrm{Exp}(\frac{1}{7})$, $E[\tau] = 7$.

```
N = poissrnd(lambda);
U = 600*rand(N,1);
sorted_U = [0; sort(U); 600];
tau = [diff(sorted_U)];

steps = find(sorted_U >= 600,1)-1;
tau = tau(1:steps);
a = 0;
b = 1000;
tall = [];
Yall = [];
kall = [];

if N>0
    for c = 1:steps
        [ts, Ys] = ode45(f,[0,tau(c)], IC);
        k = [12000 + (a+(b-a)*rand), 0, 0, 0, 0, 0];
        IC = Ys(end,:) + k;
        tall = [tall; ts+sum(tau(1:(c-1)))];
        Yall = [Yall; Ys];
        kall = [kall; k(1)];
```

Figure: exponentially sampling τ

```
number_of_lambda = 0:31;
lambda = 600./(7+number_of_lambda*3);

%for more than one lambda, need to use the code below
prob_excursion = zeros(length(number_of_lambda),number_of_trials);
results = zeros(length(number_of_lambda),number_of_trials);
for j = 1:length(lambda)

    parfor k = 1:number_of_trials
        [excursion_result(k), excursion_time(k)] = trial(lambda(j));
    end
```

Figure: for loop of lambdas

$N \sim \text{Pois}(\lambda),\ \tau \sim \text{Exp}(\frac{\lambda}{600})$

Probability of excursion

- λ represents the average number of kicks in 600 days. $\lambda = 6$
- $n = 10000$
- $\mu = \text{mean(excursion result)} \approx 0.9570$
- $\sigma = \text{std(excursion result)} \approx 0.2029$
- $CI = [y \pm \frac{\sigma}{\sqrt{n}} \times 1.96]$, where $\sigma = 0.2029$, $2000 \leq n \leq 10000$

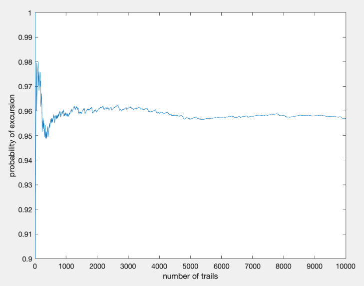


Figure: probability of excursion

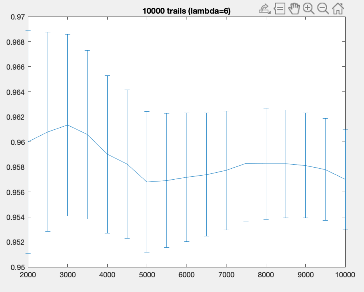


Figure: probability of excursion with errorbar

$N \sim \mathrm{Pois}(\lambda)$, $\tau \sim \mathrm{Exp}(\frac{\lambda}{600})$

How does λ influence time to excursion

- λ represents the average number of kicks in 600 days.
- $\frac{600}{\lambda}$ represents the average time between kicks. $E[\tau] = \frac{600}{\lambda}$.
- As λ increases, time to excursion is more likely to have Gaussian distribution.
- Also, as λ increases, the mean time to excursion decreases.

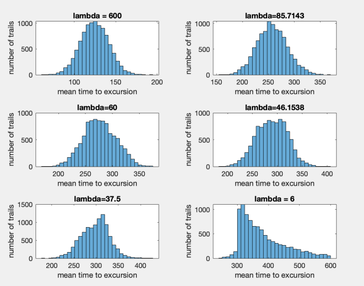


Figure: histogram of time to excursion corresponding to different lambdas

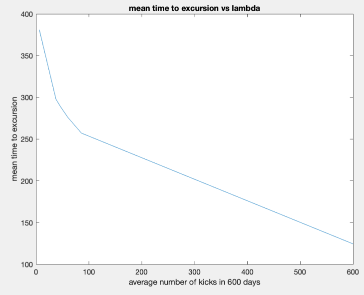
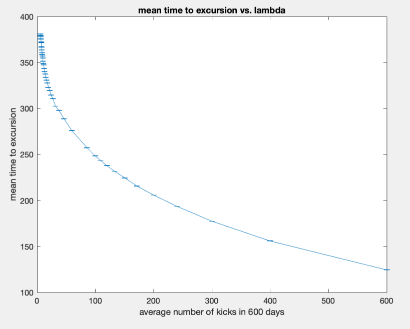


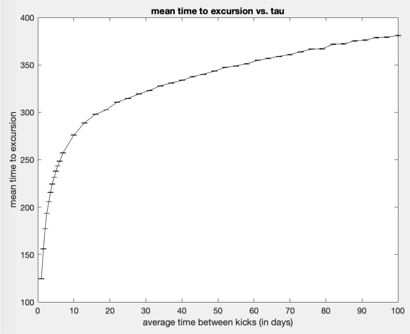
Figure: mean time to excursion vs. lambda

$N \sim \text{Pois}(\lambda),\ \tau \sim \text{Exp}(\frac{\lambda}{600})$

How does λ and τ influence the mean time to excursion

- λ represents the average number of kicks in 600 days.
- τ (i.e. $\frac{600}{\lambda}$) represents the average time between kicks. $E[\tau] = \frac{600}{\lambda}$.
- 32 points, each one corresponds to a specific λ.
- As λ increases, the mean time to excursion decreases.
- As τ increases, the mean time to excursion increases.

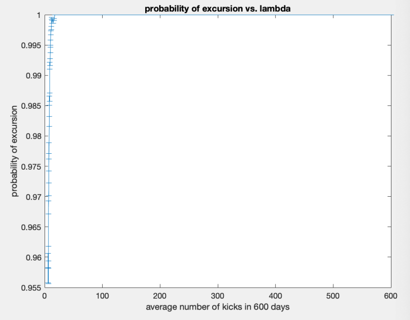


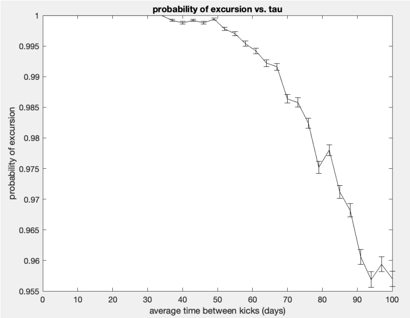


$N \sim \text{Pois}(\lambda),\ \tau \sim \text{Exp}(\frac{\lambda}{600})$

How does λ and τ influence the probability of excursion

- λ represents the average number of kicks in 600 days.
- τ (i.e. $\frac{600}{\lambda}$) represents the average time between kicks. $E[\tau] = \frac{600}{\lambda}$.
- As λ increases, the probability of excursion increases and approaches to 1.
- As τ increases, the probability of excursion decreases.
- By constructing the errorbar, we conclude it has a potential to be a smooth curve.





Future Direction for Further Exploration

- Bifurcation analysis

Thanks for listening!