Effects of Exposure Dynamics in Dose Response Relationships

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Joseph Eisenberg, James Koopman, Josep Serra
University of Michigan

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Towards a Physiologically-Based Dose – Response Model

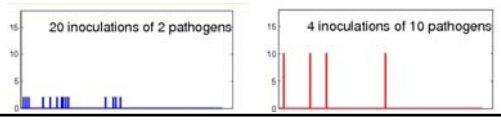
- **Rationale**
  - Low dose extrapolation
    - Empirical data only exists in high-doses
  - Understanding dominant modes of transmission
    - Optimal intervention strategies depend on which modes transmission are dominant
      - E.g., face mask vs. decontamination for influenza control

Dose Response: The Exponential Model

- Biological rationale
  - Single hit model
    - Any pathogen has some probability of infection
    - Each pathogen acts independently
    - These assumptions lead us to the exponential model for risk

$$1 - e^{-\hat{r}D}$$

- Risk depends on dose and *r*, the per pathogen risk
- **Does risk depend on time between inoculations?**

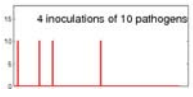


Biological Issues with Time- Independence

- Time independence
  - Implies immune system plays no role in controlling infection
- Immune system operates at time-scales ranging from minutes to weeks
- Time-scale of environmental contamination to exposure can be minutes to hours
  - The innate immune system is active at this time scale

Physiologically-based Dose Response Behavior

$$F(\{d_{t_0+i\Delta t}\}_{i=0}^{n})$$



Assumption 1:

Inoculations occur over short time period. Means doses can be summed

$$F(\{d_{t_0+i\Delta t}\}_{i=0}^{n}) = F(\sum_{i=0}^{n} d_{t_0+i\Delta t}) \text{ when } \Delta t \to 0$$

Assumption 2:

Inoculations occur over very long time period. Means risks from each inoculation are independent

$$F(\{d_{t_0+i\Delta t}\}_{i=0}^{n}) = 1 - \prod_{i=0}^{n} (1 - F(d_{t_0+i\Delta t})) \text{ when } \Delta t \to \infty$$

Assumption 3:

Inoculations occur over intermediate time periods. Means risk should decrease for longer exposure periods

$$F(\{d_{t_0+i\Delta t_i}\}_{i=0}^{n}) < F(\{d_{t_0+i\Delta t_j}\}_{i=0}^{n}) \text{ when } \Delta t_i > \Delta t_j$$

Cumulative Dose Model

- Continuous time Markov chain model can capture the needed dynamics
  - Dose has less probability of infection if the time of inoculation is longer
    - Time-dependent dose-response experiments are needed to inform the dynamics of this dose response relationship

System state variables and parameters

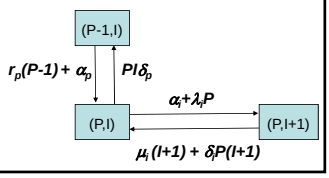
P # of pathogens
I # of immune particles

D total dose
T total inoculation time
α_p = D/T for t<T and 0 for t>T

r_p intrinsic growth rate of pathogens
δ_p deactivation rate of pathogens

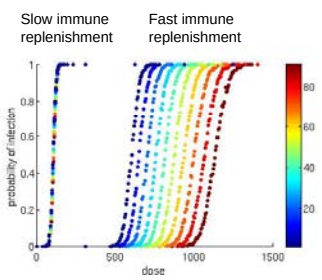
α_i arrival rate of immune particles
λ_i recruitment rate of immune particles
μ_i natural death rate of immune particles
δ_i deactivation rate of immune particles

Model description



Cumulative Dose Model: Dynamics

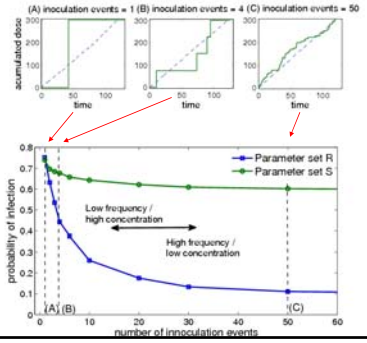
- Slow immune replenishment (α_i=0.001):
  - Dose-response function is independent of dosing time periods
- Fast immune replenishment (α_i=0.1):
  - Shorter dosing regimes shifts dose-response function to left (increased infectivity)



Blue to red transition represents longer/lower concentration dosing periods

Cumulative Dose Model: Effects of Number of Inoculations on Risk

- Three different inoculation events
  - Same total dose
- Have different risks



Conclusions

- Physiologically based dynamic dose-response models
  - Incorporate an important time dependent property of infection dynamics
    - The risk of one hundred pathogens at once is higher than the risk of one pathogen every day for one hundred days
- What impact do these dynamics have on transmission systems models and the design of interventions?
  - Integration to a transmission model is computationally infeasible
  - Need a simpler model

Simple Cumulative Dose Model

$$\frac{dD}{dt} = -\gamma D^{\alpha}$$

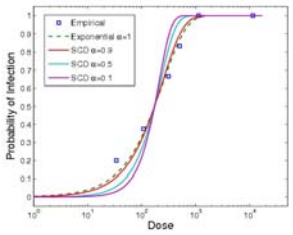
- *D* represents inoculated pathogens that are accumulated within the host
- Pathogen immune system interaction
  - Pathogens are removed due to the action of the immune system
  - The effectiveness of the immune system decreases as the number of pathogens increase
- α governs the time dependence between inoculations
  - $\alpha = 1$ is the time independent, exponential condition
  - $\alpha < 1$ is the time dependent condition
- Expect life-time of a pathogen is (*n* is the number of initial pathogens)

$$n^{\alpha}\gamma^{-1}$$

Simple Cumulative Dose Model: Single Inoculation

Single inoculation case.

$$P_{inf}(D) = 1 - e^{-s\int_0^{T_e} D(t)dt}$$



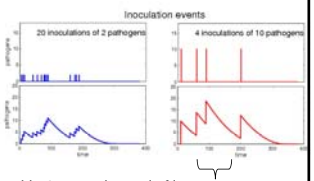
Where

- T_e, the time to extinction of pathogens, is a function of the immune system (α,γ) and pathogen (*r*)
- ***s***, the risk associated to a single pathogen that persists over time, is function of the immune system (α,γ) and pathogen (*r*)

Simple Cumulative Dose Model: Multiple Inoculation

Multiple inoculation case

$$P_{inf}(D) = 1 - e^{-s\int_0^{\infty} D_m(t)dt}$$



The same total dose of pathogens inoculated in 4 events instead of in 20 events persist longer, and therefore, give a higher risk of infection

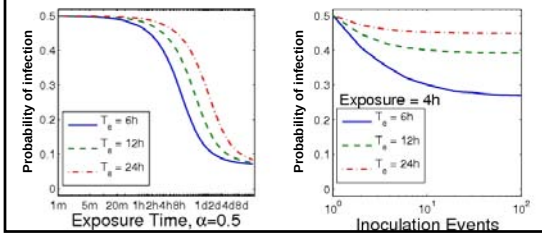
Total dose is the sum of each inoculation

Dose from each inoculation is a function of the prior dose

$$\int_0^{\infty} D_m(t)dt = \sum_{i=1}^{n-1}\left[\int_0^{t_{i+1}-t_i} D(t, D(t_i)+d_i)dt\right] + \int_0^{\infty} D(t, D(t_n)+d_n)dt$$

Simple Cumulative Dose Model: Qualitative Behavior

- This simple cumulative dose model exhibits similar behavior as the more complex pathogen-immune interaction model
  - Risk decreases as exposure time or inoculation events increase



Incorporating Dynamic Dose-Response Functionality in a Transmission Model

- The classical SIR model does not take into account environment

$$\frac{dS}{dt} = -\beta SI \qquad \frac{dS}{dt} = -Sf(E) \qquad \frac{dE}{dt} = g(I)$$

- To model environmental exposure a dose-response function, ***f***, is required to determine infectivity

Incorporating Dynamic Dose-Response Functionality into a Transmission Model

- If immune system impacts the risk of infection
  - The probability of becoming infected is calculated as a function of the current level of pathogen within the host.
  - The number of pathogens in individual *i* residing in cell *j* evolves as a function of fomite pickup, C_{fj}, airborne pickup, C_{aj}, and die off within host

$$D_i \begin{cases} + \text{ pickup } C_{f,j} \text{ at } \textit{self-inoculation} \text{ rate} \\ + \text{ pickup } C_{a,j} \text{ at } \textit{breathing} \text{ rate} \\ -1 \text{ at a rate } \gamma D_i^{\alpha} \end{cases}$$

  - The per capita force of infection at every *dt* is a function of pathogen infectivity, *r*, and immune system dynamics, ***α***, ***γ***
    - *f(E)* from previous slide becomes

$$\hat{r}\gamma(2-\alpha)\left(\frac{\log(\frac{1}{2})}{-\hat{r}}\right)^{\alpha-1} D_i dt$$

Incorporating Dynamic Dose-Response Functionality into a Transmission Model

- How do the dose response dynamics impact fomite vs. airborne transmission?
- Simulation scenario (assumptions)
  - Same $TCID_{50}$ for fomite and airborne
  - Contamination is constant
  - Same dose received via fomite and air
  - These assumptions are all wrong, but allows us to compare the relative impacts of fomite and airborne routes of transmission

Risk	α=1 $TCID_{50}$=3.2	α=0.5, T_e=12h ID_{50}=64	α=0.1, T_e=12h, ID_{50}=64	α=0.1, T_e=12h, ID_{50}=640	α=0.1, T_e=12h, ID_{50}=6400
R_{total}	0.2	0.1	0.03	0.04	0.04
R_{fomite}	0.11	0.05	0.02	0.03	0.03
R_{air}	0.11	0.02	0.003	0.0005	0.0001
R_{fomite}/ R_{air}	1.0	2.0	7.6	52	366

Conclusions

- Dynamic dose-response models can capture the immune system impact on infection
  - The crucial issue is the time course of exposure
    - The risk of exposure of one hundred pathogens at once is not same as the risk of exposure of one pathogen every day for one hundred days
- Implications
  - Risk of infections are more accurately captured
    - Immune system serves to attenuate the impact of low-level longer term exposure
  - Since temporal patterns of exposure differ by route of transmission, the dose response relationship can impact intervention strategies
    - Fomite exposure has fewer but higher magnitude inoculation events
    - Airborne exposure has more but lower magnitude inoculation events