Importance of Nested Models in Modeling Infectious Diseases

Conference Paper · July 2017

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IMPORTANCE OF NESTED MODELS MODELING INFECTIOUS DISEASES

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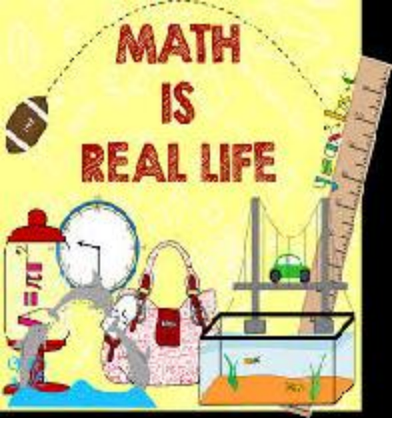
4th Strathmore International Mathematics Conference (SIMC 2017):
19^{th}-23^{rd} June 2017

Outline

- Introduction
- Background
- Importance of nested models in modeling infectious diseases
- Within host influenza A virus and pnuemococcus bacteria
- Conclusion



Motivation

- ``Mathematics is much more than a language for dealing with the physical world. It is a basis of models and abstractions which will enable us to obtain astonishing new insights into the way in which nature operates. In fact, the prettiness and elegance of the physical laws themselves are only evident when expressed in a proper mathematical framework." –Melvin Schwartz (1932–2006)
- ``Where there is life there is a model, and where there is a model there is mathematics. Once that germ of rationality and order exists to turn a chaos into a cosmos, then so does mathematics. There could not be a non-mathematical Universe containing living observers.'' – John D. Barrow (1995)
- ``There is no branch of mathematics, however abstract which may not someday be applied to the phenomena of the real world-.''–Nicolai Lobachevsky (1792–1856)

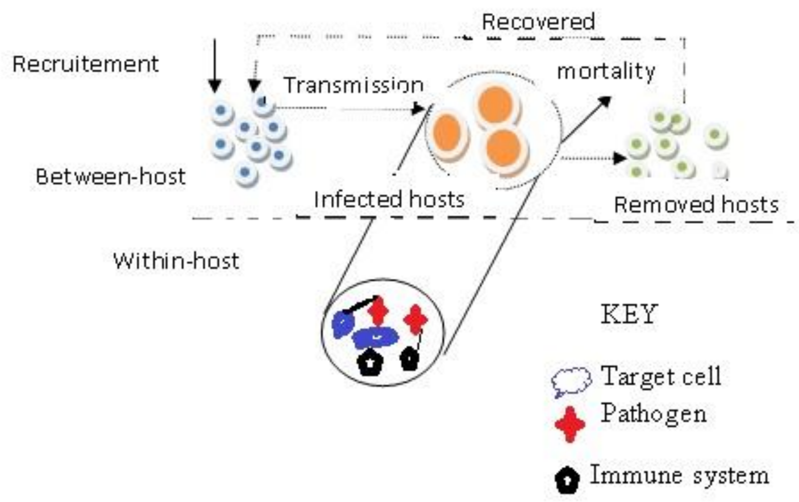
``Remember that all models are wrong; the practical question is how wrong they have to be to not be useful.''
George E.P.Box (1919–2013)

INTRODUCTION

- Mathematics has far reaching repercussion on lives of living organisms.
- 1st publication addressing the mathematical modeling of epidemics dates back in 1760 by Daniel Bernoulli's analysis of smallpox Siettos & Russo (2013) .
- Use of nested models for linking levels of disease dynamics has recently become more common, focusing on nesting model of within-host kinetics with between-host epidemiological dynamics.

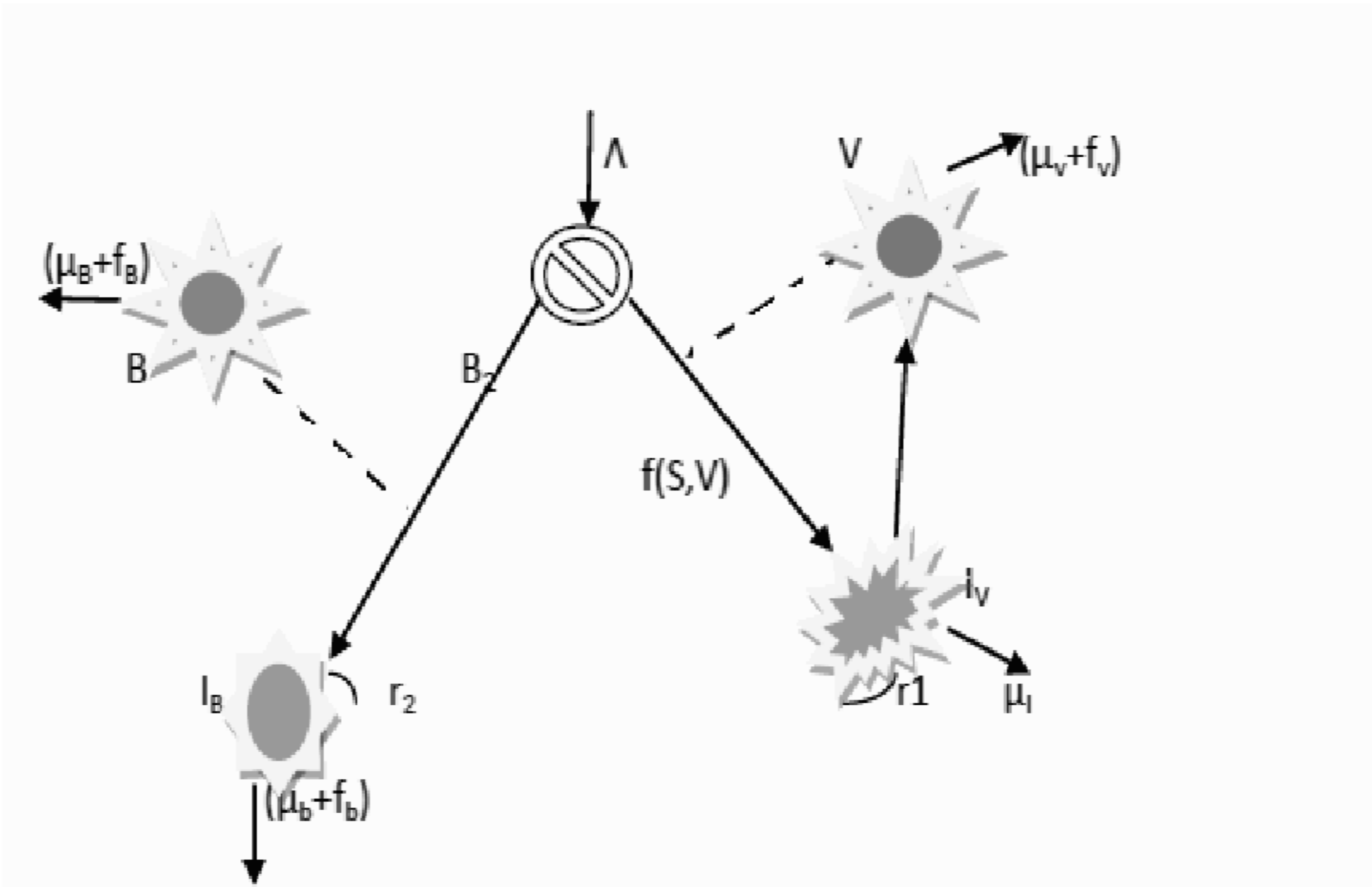
Introduction cont'd

- The threat by infectious diseases will persist, and human mortality attributed to infection is projected to remain at current levels of 13 to 15 million deaths annually until at least 2030()



A schematic representation for Within-host and between - host

A compartmental diagram for the within host IAV and SP interaction



S–I–V–B MODEL

$$N(t) = S(t) + I_V(t) + I_B + V(t) + B(t) \quad [1]$$

$$\dot{S} = \Lambda - (f(S,V) + \beta_2 SB + \mu_s S) \quad [2]$$

$$\dot{I}_V = f(S,V) + (r_1 - \mu_I)I_V \quad [3]$$

$$\dot{V} = \tau_1 I_V - (\mu_v + f_v)V \quad [4]$$

$$\dot{I}_B = \beta_2 BS - (\mu_b + f_b)I_B \quad [5]$$

$$\dot{B} = r_2 V(1 - \frac{V+dB}{K}) + (\tau_B - \mu_B - f_B)B \quad [6]$$

Where $f(S,V) = \frac{\beta_1 SV}{1+aS+bV}$ (Beddington–DeAngelis infection rates

(Beddington, 1975)

The corresponding eigen values are $\lambda_1 = \lambda_2 = 0, \lambda_3 = \frac{\beta_2 \Lambda}{(\mu_c + a\Lambda)(\mu_B + f_B)}, \lambda_4 = \frac{\beta_1 \tau \Lambda}{(\mu_c + a\Lambda)(\mu_v + f_v)(\mu_I - r_I)})$

The spectral radius$= \text{Max}\{\lambda_i\}|_{i=1,2,3}$

Hence $T_0 = Max\{T_0^B, T_0^V\} = Max(\frac{\beta_2 \Lambda}{(\mu_c + a\Lambda)(\mu_B + f_B)}, \frac{\beta_1 \tau \Lambda}{(\mu_c + a\Lambda)(\mu_v + f_v)(\mu_I - r_I)}$

Global stability analysis of the infection free

If $T_0 < 1$, the infection –free state E_0^* is globally asymptotically stable on $\mathbf{R}_+^5$

Considering the stability of infection free–state E_0 in $\bar{\Omega}$ under the condition $T_0 < 1$.
We use the general form $y - y_0 - y_0 ln\frac{y}{y_0}$ and $S - S_0 - \int_{S_0}^{S} \frac{f(S_0, I_0)}{f(\tau, I_0)} d\tau$ to construct suitable lyapunov functions and apply (Theorem 3.3) of on nonlinear incidence rate. Korobeinikov,2007)

Global dynamics when $T_0 > 1$

Theorem: *If $T_0 > 1$, then the unique endemic equilibrium is globally asymptotically stable. The basic reproduction number is given by*

$$T_0 = Max\left(\frac{\beta_2 \Lambda}{(\mu_c + a\Lambda)(\mu_B + f_B)}, \frac{\beta_1 \tau \Lambda}{(\mu_c + a\Lambda)(\mu_v + f_v)(\mu_I - r_I)}\right)$$

Proof

$$L_{EE} = S - \int_S^{*S} \frac{f(S,V)}{f(\tau,V)} d\tau + (I_v - I_v^* ln I_v) + V - V^* ln V + (I_B - I_B^* ln I_B)$$

$$\dot{L}_1 = \frac{f(S^*,V)}{f(S,V)}[\Lambda - (f(S,V) + \beta_2 SB + \mu_s S)]$$

substituting for fo the endemic state for Λ

We obtain $\frac{f(S^*,V)}{f(S,V)}[f(S^*,V^*)(1 - \frac{f(S,V)}{f(S^*,V*)}) + \beta_2 S^* B^*(1 - \frac{SB}{S^* B^*}) + \mu_s S^*(1 - \frac{S}{S^*})]$

Hence $f(y_i) = 1 - y_i + ln y_i|_{(i=1,2,3)} < 0$ whenever $y_i > 1$

Clearly $\dot{L}_1 < 0$ and $L_1 = 0$ for $SB = S^* B^*$, $S = S^*$,$f(S,V) = f(S^*,V^*)$

GAS cont'd

We consider Vertex 2

$\dot{L}_2 = (1 - \frac{I_v^*}{I})(f(S,V) + (r_I - \mu_I)I_v)$

$\dot{L}_2 = (1 - \frac{I_v^*}{I_v})f(S,V) - (1 - \frac{I_v^*}{I_v})(\mu_I - r_1)I_v$

Since the arithmetic mean is greater than the geometric mean then $\dot{L}_2 \leq (1 - \frac{I_v^*}{I_v})f(S,V)$

Therefore $\dot{L}_2 \leq 0$ if $I_v = I_v^*$

Consider vertex 3

$L_3 = V - V^* lnV$

$\dot{L}_3 = (1 - \frac{V^*}{V})(\tau_1 I_v - (\mu_v + f_v)V)$

$\dot{L}_3 = \tau_1 I_v - (\mu_v + f_v)V - \frac{V^*}{V}\tau_1 I_v + (\mu_v + f_v)V^*$

$\dot{L}_3 = \tau_1 I_v(1 - \frac{V^*}{V}) + V^*(\mu_v + f_v)(1 - \frac{V}{V^*})$

$\dot{L}_3 = 0$ if $V^* = V$ and if we let $x_1 = \frac{V^*}{V}$ such that $f(x_1) = 1 - x_1 + lnx_1$ and $x_2 = \frac{V}{V^*}$ such that $f(x_2) = 1 - x_2 + lnx_2$

$\dot{L}_3 < 0$ if $x_1, x_2 > 1$.

GAS cont'd

Consider vertex 3

$L_3 = P_1 - P_1^* ln P_1$

$\dot{L}_3 = (1 - \frac{P_1^*}{P_1})(\tau I - (\mu_1 + f_1)P_1)$

$\dot{L}_3 = \tau I - (\mu_1 + f_1)P_1 - \frac{P_1^*}{P_1}\tau I + (\mu_1 + f_1)P_1^*$

$\dot{L}_3 = \tau I(1 - \frac{P_1^*}{P_1}) + P_1^*(\mu_1 + f_1)(1 - \frac{P_1}{P_1^*})$

$\dot{L}_3 = 0$ if $P_1^* = P_1$ and if we let $x_1 = \frac{p_1^*}{P_1}$ such that $f(x_1) = 1 - x_1 + ln x_1$ and $x_2 = \frac{P_1}{P_1^*}$ such that $f(x_2) = 1 - x_2 + ln x_2$

$\dot{L}_3 < 0$ if $x_1, x_2 > 1$.

Consider Vertex 4

$\frac{\partial L_4}{\partial P_2} = 1 - \frac{P_2^*}{P_2}$ and $\dot{L}_4 = (1 - \frac{P_2^*}{P_2})(P_1 r_2(1 - \frac{P_1 + dP_2}{K}) + \beta_2 C P_2 - (\mu_2 + f_2)P_2)$

$$\dot{L}_4 = (P_1 r_2(1 - \frac{P_1 + dP_2}{K}) + \beta_2 C P_2 - (\mu_2 + f_2)P_2) - (P_1^* r_2(1 - \frac{P_1 + dP_2}{K}) + \beta_2 C^* P_2^* - (\mu_2 + f_2)P_2^*)$$

$$\dot{L}_4 = P_1 r_2(1 - \frac{P_1 + dP_2}{K})(1 - \frac{P_2}{P_2^*}) + \beta_2 P_2^* C(\frac{P_2}{P_2^*} - 1) + (\mu_2 + f_2)P_2^*(1 - \frac{P_2}{P_2^*})$$

GAS cont'd

Consider vertex 4

$\dot{L}_4 = (1 - \frac{I_B^*}{I_B})(\beta_2 BS - (\mu_b + f_b))I_B$

Hence $I_B^*(\mu_b + f_b)(1 - \frac{I_B}{I_B^*}) - \beta_2 BS(1 - \frac{I_B^*}{I_B})$

This implies that $\dot{L}_4 \leq 0$

Consider Vertex 5

$\frac{\partial L_5}{\partial B} = 1 - \frac{B^*}{B}$ and $\dot{L}_4 = (1 - \frac{B^*}{B})(Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - \mu_2 - f_2)B)$

$\dot{L}_5 = (Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - \mu_B - f_B)B) - (\frac{B^*}{B}Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - (\mu_B + f_B))B^*)$

$$\dot{L}_5 = Vr_2(1 - \frac{V+dB}{K})(1 - \frac{B^*}{B}) + (\tau_2 - \mu_B - f_B)B + \tau_2 - \mu_B - f_B)B^*$$

$$\dot{L}_5 = Vr_2(1 - \frac{V+dB}{K})(1 - \frac{B^*}{B}) - (\tau_2 + \mu_B + f_b)B^*[(\frac{B}{B^*}) + 1]$$

Clearly $\dot{L}_5 \leq 0$

$and \dot{L}_5 = 0$ if $B = B^*$

GAS cont'd

Consider Vertex 5

$\frac{\partial L_5}{\partial B} = 1 - \frac{B^*}{B}$ and $\dot{L}_4 = (1 - \frac{B^*}{B})(Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - \mu_2 - f_2)B)$

$\dot{L}_5 = (Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - \mu_B - f_B)B) - (\frac{B^*}{B}Vr_2(1 - \frac{V+dB}{K}) + (\tau_2 - (\mu_B + f_B))B^*)$

$$\dot{L}_5 = Vr_2(1 - \frac{V+dB}{K})(1 - \frac{B^*}{B}) + (\tau_2 - \mu_B - f_B)B + \tau_2 - \mu_B - f_B)B^*$$

$\dot{L}_5 = Vr_2(1 - \frac{V+dB}{K})(1 - \frac{B^*}{B}) - (\tau_2 + \mu_B + f_b)B^*[(\frac{B}{B^*}) + 1]$

Clearly $\dot{L}_5 \leq 0$

$and \dot{L}_5 = 0$ if $B = B^*$

Using the comparison between the arithmetical and the geometrical means we see that $\dot{L}_5$ is negative definite. Thus, if $S^*, I_V^*, I_B V^*, B^* > 0$ then $\dot{L}_{EE} = \sum_{i=1}^{4} \dot{L}_i \leq 0$ for all $S, I_V, I_B V, B > 0$, hence the singleton E^* is the only invariant set in $\{(S^*, I_V^*, I_B^*, B^*) : \dot{L}_{EE} = 0\}$. We can thus conclude that the global stability of E^* is induced by LaSalle's principle. This ends the proof of the theorem.

With the above description of variables/parameters and assumptions we use the integro–differential equations to generate the equations of the model based on [32].

$$\dot{S} = \phi R - S\int_0^\infty \beta(V(a))I(a,t)da$$

$$\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = S\int_0^\infty \beta(V(a))I(a,t)da - (\gamma(a) + m(a))I(a,t)$$

$$I(0,t) = S(t)\int_0^\infty \beta(V(a))I(a,t)da$$

$$\dot{R} = \int_0^\infty \gamma(a)I(a,t)da - \phi R$$

Where $m(a) = m_0 + \alpha(a)$ is the mortality rate of the host at infection age a, m_0 is the natural death rate of infected individuals, $\alpha(a) = r^{\epsilon}P(a)$ is the host mortality due to the pathogen with a hypothesis that the virulence is dependent on the replication rate. ϵ is a measure of the efficiency of replication.

Conclusion

- Important to consider linking within-host models with between -host models to clearly understand the dynamics of the disease process
- The threshold quantities (R0), for the nested models give a good interpretation on the new infections generated in both organizations.

PAU

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