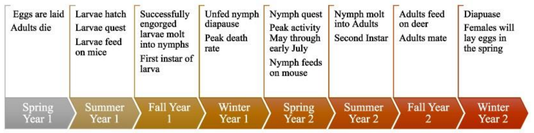
Tick-Mouse Models for Lyme Disease with Seasonal Variations in Births, Deaths, and Tick Feeding

Kat Husar, Dana Pittman, Johnny Rajala

TEXAS TECH UNIVERSITY

Background Biology

- Lyme disease #1 vector-borne disease in the United States.
  - Spreading north to Canada
- *Ixodes scapularis* (black legged-tick) infected with *Borrelia burgdorferi.*
- *I. scapularis* feeds on white-footed mouse, understanding this interaction is critical because the mice are competent.
- The cycle of infection is driven by larvae feeding on infected mice molting into infected nymphs then transmitting the disease to another susceptible host such as a mouse or human.



Parameters

Table 1: Parameters and their biological meaning

Parameter	Description	Units *	Value
b_T	Tick birth rate and survival per adult	larva · adult^{-1}	3000
β_L	Larva feeding rate	larva · (day · mouse)$^{-1}$	0.08
β_N	Nymph feeding rate	nymph · (day · mouse)$^{-1}$	0.002
β_A	Adult feeding rate	adult · (day · deer)$^{-1}$	0.56
e_L	Survival during larva to nymph transition	–	0.9
e_N	Survival during nymph to adult transition	–	0.9
e_A	Survival during adult molting period	–	0.58
μ_L	Death rate of larvae	day^{-1}	0.003-0.006
μ_N	Death rate of nymphs	day^{-1}	0.002-0.006
μ_A	Death rate of adult ticks	day^{-1}	0.0001-0.006
τ_L	Time it takes for larva to molt into a nymph	day	21.5
τ_N	Time it takes for nymph to molt into an adult	day	26
τ_A	Delay time between adult laying eggs and larva emerging	day	180
b_M	Mouse birth rate	day^{-1}	0.03
d	Death rate of mice	day^{-1}	0.012
d_D	Density dependent mice death rate	day^{-1}	0.001
β_{TM}	Transmission rate from tick to mouse	(day · nymph)$^{-1}$	–
a_L	Half the maximum number of larvae per km^2	larva	6500
a_N	Half the maximum number of nymphs per km^2	nymph	6500
a_A	Half the maximum number of adult ticks per km^2	adult	6500

* Parameters with no units are marked with dash

Periodicity

- Periodicity mimics seasonality
  - Tick birth, feeding activity for all tick stages, death of all species
- Below are example equations for larval stage

Tick Birth:

$$b_T(t) = \max\left(A_b(2+\sqrt{2})\sin(\frac{\pi}{180}(t-45)\right) - A_b(\sqrt{2}+1), 0)$$

Feeding:

$$\beta_L(t) = \max\left(A_l(2+\sqrt{2})\sin(\frac{\pi}{180}(t-45)\right) - A_l(\sqrt{2}+1), 0)$$

Death:

$$\mu_L(t) = -\frac{A_{lmax}-A_{lmin}}{2}\sin(\frac{\pi}{90}t) + \frac{A_{lmax}-A_{lmin}}{2}$$

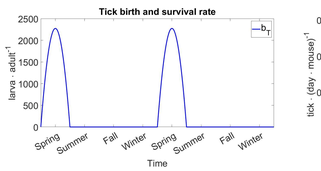


Figure: Tick Birth
Peak birth occurs in middle of spring.

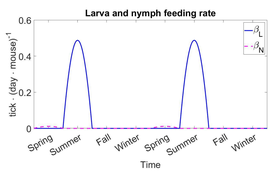


Figure: Larva and Nymph Feeding Rate
Larva peak in summer. Nymphs peak during the spring.

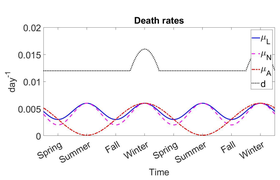


Figure: Death Rates
All species have peak death in the winter. Larva and nymph experience second peak during summer.

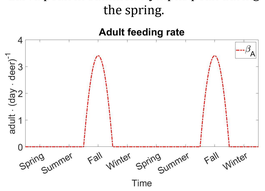


Figure: Adult Feeding
Adults peak during the fall.

DDE Model

Tick:

$$\dot{L}(t) = b_T(t)\beta_A(t-\tau_A)e_A(t)\frac{A(t-\tau_A)D}{a_3+A(t-\tau_A)} - \beta_L(t)\frac{L(t)\left(M^S(t)+M^I(t)\right)}{a_1+L(t)} - \mu_L(t)L(t)$$

$$\dot{N^S}(t) = \beta_L(t-\tau_N)e_L(t)\frac{L(t-\tau_L)M^S(t-\tau_L)}{a_1+L(t-\tau_L)} - \beta_N(t)\frac{N^S(t)\left(M^S(t)+M^I(t)\right)}{a_2+N^S(t)+N^I(t)} - \mu_N(t)N^S(t)$$

$$\dot{N^I}(t) = \beta_L(t-\tau_N)e_L(t)\frac{L(t-\tau_L)M^I(t-\tau_L)}{a_1+L(t-\tau_L)} - \beta_N(t)\frac{N^I(t)\left(M^S(t)+M^I(t)\right)}{a_2+N^S(t)+N^I(t)} - \mu_N(t)N^I(t)$$

$$\dot{A}(t) = \beta_N(t-\tau_N)e_N(t)\frac{N^I(t-\tau_N)+N^S(t-\tau_N)}{a_2+N^S(t-\tau_N)+N^I(t-\tau_N)}\left(M^S(t-\tau_N)+M^I(t-\tau_N)\right) - \beta_A(t)\frac{A(t)D}{a_3+A(t)} - \mu_A(t)A(t)$$

See DDE compartmental diagram for mouse equations.

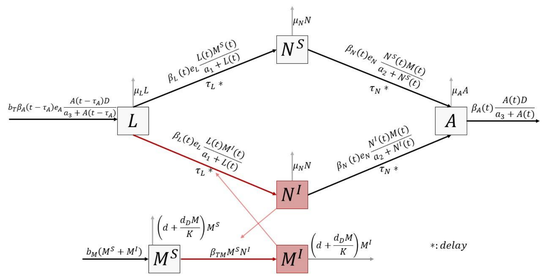


Figure: Compartmental Diagram of ODE

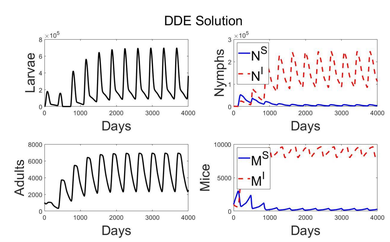


Figure: DDE Solution
DDE model converging to periodic solution. Converges around 1500 days.

ODE Model

See the compartmental diagram for equations of ODE.

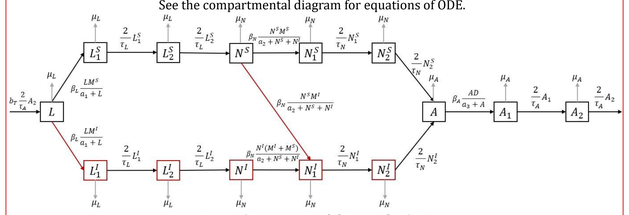


Figure: Compartmental diagram for ODE

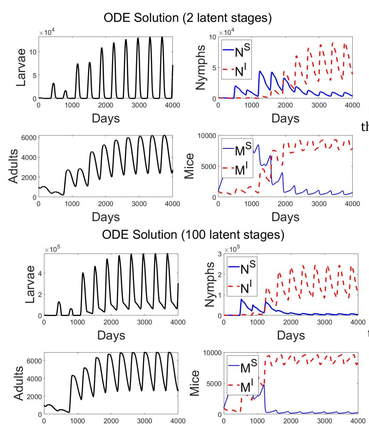


Figure: ODE n=2
Converges to periodic solution slower than DDE solution. Smaller population of nymphs than DDE solution. Converge around 3000 days.

Figure: ODE n=100
Converges to periodic solution quicker than ODE n=2 due to faster $\frac{n}{\tau}$ transition. This solution more closely mimics the DDE solution. Converges around 2000 days.

CTMC Model

- Continuous-time Markov chain (CTMC) is a stochastic model, probability a given event will occur.
- The CTMC model and ODE model share parameters, but their dynamics are different.

Event	Description	Transitions	Rate*
1	Birth of Larva	$L \to L+1$	$b_T\frac{a_1}{\tau_L}A_n$
2	Death of Larva	$L \to L-1$	$\mu_L L$
$3+1_{j=I}$	Larvae feeds on susceptible[a] or infected[b] mouse	$L \to L-1$; $L_1^j \to L_1^j+1$	$\beta_L\frac{LM^j}{a_1+L}$
$4+k^c+(n-1)1_{j=I}$	Susceptible[a] or infected[b] larvae transition during time delay	$L_k^j \to L_k^j-1$; $L_{k+1}^j \to L_{k+1}^j+1$	$\frac{n}{\tau_L}L_k^j$
$2n+2+k^d+n1_{j=I}$	Susceptible[a] or infected[b] larvae death during delay stage	$L_k^j \to L_k^j-1$	$\mu_L L_k^j$
$4n+3+1_{j=I}$	Transition from susceptible[a] or infected[b] larva to susceptible or infected nymph	$L_n^j \to L_n^j-1$; $N^j \to N^j+1$	$\frac{n}{\tau_L}L_n^j$
$4n+5+1_{j=I}$	Susceptible[a] or infected[b] nymph death	$N^j \to N^j-1$	$\mu_N N^j$

Figure: Sample of general form events (total events 21)

- The CTMC is probabilistic; therefore, there are times the infection will die out or the spread of the infection happens faster than the deterministic ODE model.
- The probabilistic method is best for the introduction of a disease into a new area.

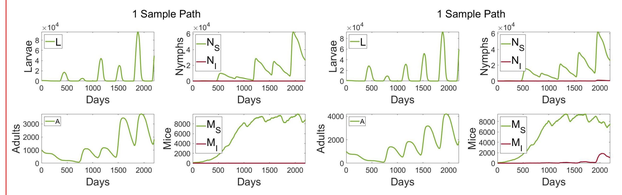


Figure: LOW INFECTION
The infection dying out, there is an outbreak.

Figure: LOW INFECTION
The infection persists. Near day 1500 the mouse infection begins to appear.

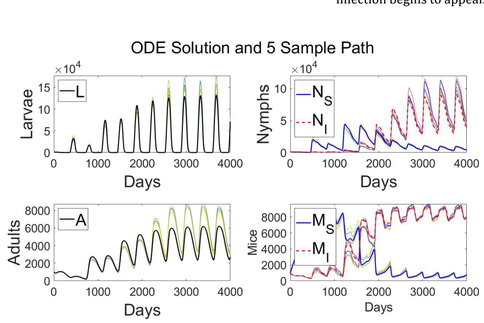


Figure: HIGH INFECTION
CTMC paths with ODE approximation.

- The ODE is the average of the CTMC, but lacks variability seen in nature.
- Disease extinction: run 1000 simulations with ($N_I(0)$ =10) and count times all the infected states = 0.
- 450 simulations had the disease die out. Approximate probability of disease extinction 0.45.

R_0

The basic reproduction number is a well-known threshold in epidemic models, denoted as R_0. Biologically, this threshold is defined as the number of secondary infections caused by one infectious individual in an entirely susceptible population. If R_0 exceeds unity, then the number of infections will grow over time, but if it is less than unity, the number will decline. Hence, the magnitude of R_0 provides knowledge about the growth rate of infectious individuals at the start of an epidemic.

- Identify all the infected and noninfected states and the stable disease-free solution (DFS).
- Linearize the differential equations for the infected states (vector X) about the DFS:

$$\dot{X} = J(x)X = \left(F(t)-V(t)\right)X, \qquad where\ J\ is\ the\ Jacobian\ matrix\ at\ DFS$$

- Find the fundamental matrix solution $Y(t) = \Phi(t,\lambda)$ pf the linear matrix system:

$$\dot{Y} = \left(\frac{F(t)}{\lambda} - V(t)\right)Y, \qquad Y(0) = Id$$

- $R_0 = \lambda$ if $\rho\left(\Phi(\omega,\lambda)\right) = 1$, where ω is the period and ρ is the spectral radius function.
- We get $R_0 \approx 3.339$.

The basic reproduction number as a threshold for the n-stage ODE model is also a threshold for the n-stage CTMC model. If the basic reproduction number R0 < 1, the ODE model predicts that no major outbreak will occur. However, if R0 > 1, the ODE always predicts a disease outbreak, but in the CTMC model this is not always the case. In the CTMC model, there is a positive probability p of a disease outbreak and a probability of 1 – p of no disease outbreak.

Sensitivity Analysis

To determine the relative importance of each parameter, we conduct a sensitivity analysis to see which parameter has the largest effect on R0. We do this using the elasticity index of R0 with respect to each parameter, as described in [22]. For a parameter p, the elasticity index is defined as

$$r_p^R = \frac{\partial R}{\partial p}\frac{p}{R}$$

For our study, we take R to be R0. In this case, we find the R0 using parameters from Table 3, and calculate it when each individual parameter is increased by 10% and again when each parameter is decreased by 10%. This simplifies our approximation to:

$$r_p^{R_0} \approx \frac{\Delta R_0}{0.1R_0}$$

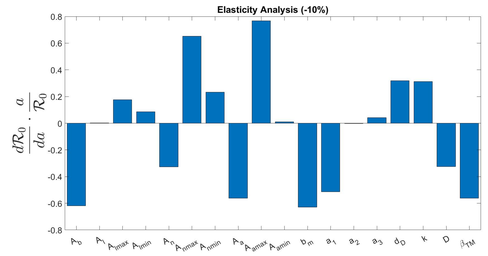


Figure: Elasticity analysis parameter decreased by 10%

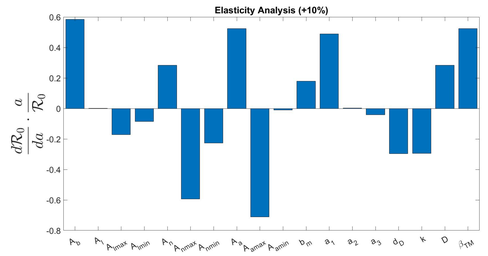


Figure: Elasticity analysis with parameter increased by 10%.

- **Most impact**: A_{amax} maximum death rate of the adult stage, A_{nmax} maximum death rate of the nymph stage, $A_b$the maximum number of eggs deposited, and the β_{TM} transmission rate from tick to mouse.
- Value changes related to parameters **controlling reproduction**, A_{amax} and A_b.
- Modification of **infection transmission** have high R_0 impact such as A_{nmax} and β_{TM}.
- **Least impact**: A_l the maximum feeding transition rate of larvae, A_{amin} the minimum death rate of adults, and a_2 half the maximum number of nymphs per square kilometer.

Future Work

- Add mast cycles.
  - This addition of fluctuation changes the amount of food available to the mouse population.
- Add branching process approximation of the CTMC model that provides an analytical approximation of the probability of an outbreak that is dependent on the time infection is introduced and number of infected nymphs and mice.
- Investigating the 100-stage ODE further with an in-depth elasticity analysis.
  - We believe 100-stage ODE solution has potential to mimic the tick dynamics more thoroughly than DDE solution.

References

The link to complete reference list: https://bit.ly/37apMuC
Contact us if there are questions about the code.

Acknowledgements

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Contact Information

Kat Husar: hussar.7@osu.edu Ohio State University - Columbus, Ohio
Dana Pittman: dana.pittman@wsu.edu Washington State University - Pullman, Washington
Johnny Rajala: johnny.rajala.2019@gmail.com University of Maryland – College Park, Maryland