Global Dynamics of an Infinite Dimensional Epidemic Model with Nonlocal State Structures

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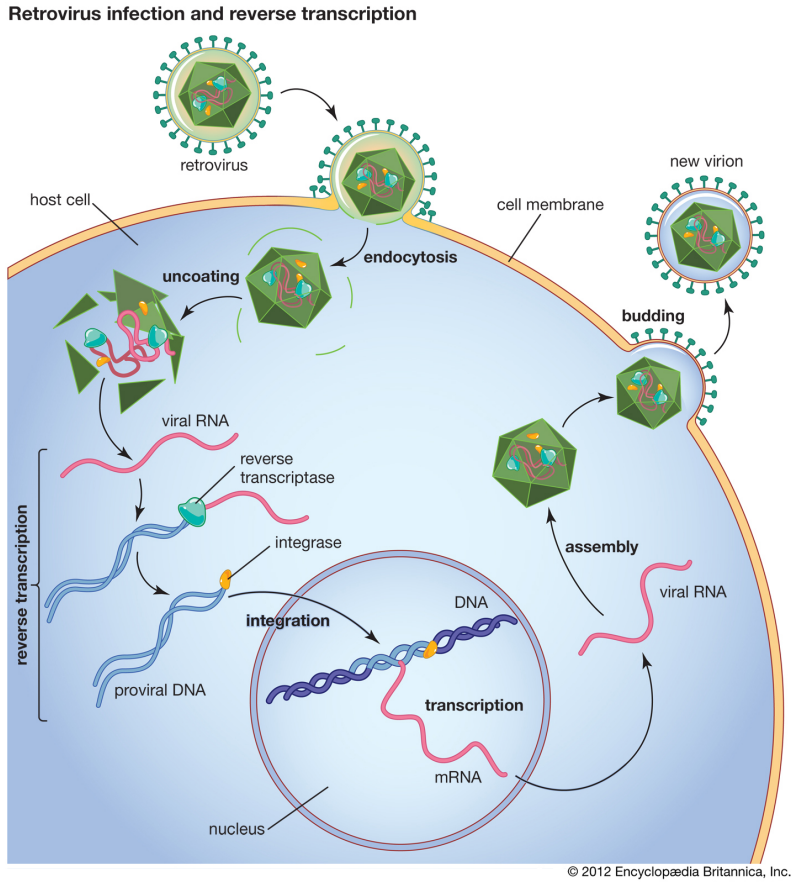
Workshop on Differential Equations & Applications
University of Central Florida, 2018

Outline

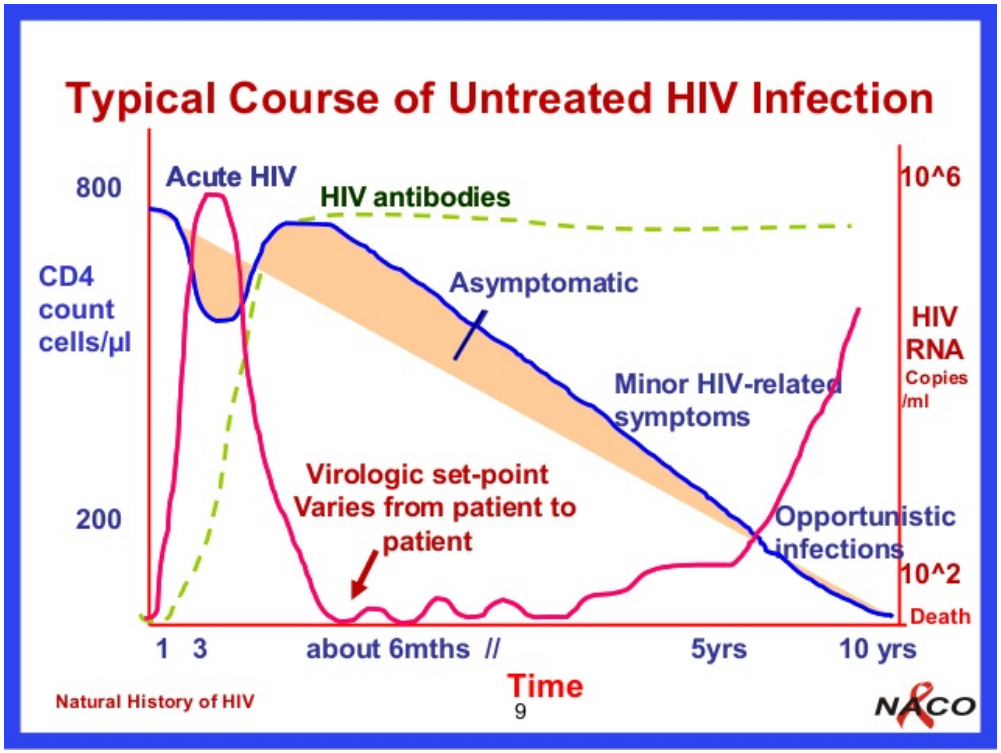
- What is "State" in an infection process: HIV as an example
  - At the microscopic level: infected cells
  - At the population level: infected individuals
  - Manifestations of state of infection
  - Impact of infection states on transmission, immune responses, and treatment strategies
- A continuous state-structured model with nonlocal effects
  - Model formulation and nonlinear semigroup
  - Asymptotic smoothness and global attractor
  - Threshold operator and the basic reproduction number $\mathbf{R}_0$
  - Linear stability analysis and $\mathbf{R}_0 = 1$ as a threshold value
  - Global stability and uniqueness of the endemic equilibrium
- Summary

State of Infection: at Microscopic Level



- The state of an infected cell = its level of viral productivity
- Cell cycles and antiviral actions can revert productivity to latent.
- Antigenic stimulations can cause activation and increase viral productivity (kick-and-kill strategy)

State of Infection: at Population Level



Source: SlideShare at Linkedin.

- The HIV state of an infected individual can be indexed by the CD4 count or/and the viral (proviral) load.
- ART treatment can change an individual's HIV state.
- Elite controllers, non-progressors, and fast progressors.

State of Infection: HIV as an Example

Key points for modeling:

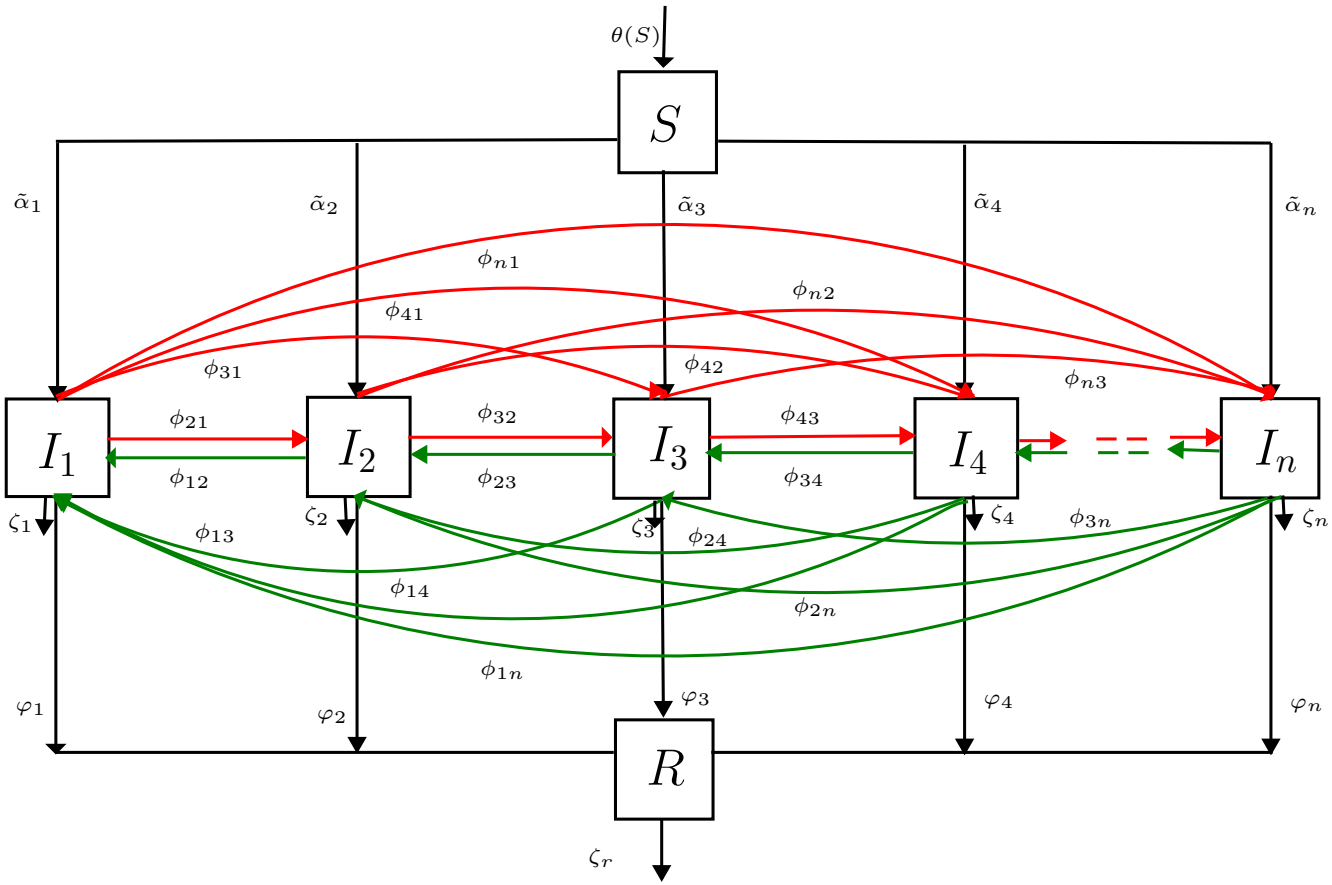
- Each infected individual has an index for the state of infection
- States correlate to infectivity, immune responses, and ART treatment strategies, and a potential cure.
- States can both progress (forward) or revert (backward).

Two modeling approaches:

- Discrete states: staged models, large systems of ODEs
- Continuous states: differential-integral models, with non-local terms.

Discrete State Models

- Group states into distinct discrete stages: I_k, $k = 1, \cdots n$.
- Consider individual transfers among different stages



(Guo-Li-Shuai (SIAP 2012), Liu-Li (2018))

A General Discrete-State Model

The model is a system of $n+1$ ordinary differential equations:

$$S' = \theta(S) - f(N)\sum_{j=1}^{n} g_j(S, I_j),$$

$$I_i^{'} = \alpha_i f(N)\sum_{j=1}^{n} g_j(S, I_j) + \sum_{j=1}^{n} \phi_{ij}(I_j) - \sum_{j=1}^{n} \phi_{ji}(I_i) - \varphi_i(I_i) - \zeta_i(I_i),$$

$$i = 1, 2, \cdots, n.$$

$$N = S + I_1 + \cdots + I_n. \quad \sum_{i=1}^{n} \alpha_i = 1.$$

Transfer Matrix

In the special case $\phi_{ij}(I_j) = \delta_{ij} I_j,\ i < j,\ \phi_{ij}(I_j) = \gamma_{ij} I_j,\ i > j,$
the matrix of transfer rates among different stages is:

$$A = \begin{bmatrix} 0 & \delta_{12} & \cdots & \delta_{1n} \\ \gamma_{21} & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \delta_{(n-1)n} \\ \gamma_{n1} & \cdots & \gamma_{n(n-1)} & 0 \end{bmatrix}.$$

Earlier staged progression models only considered tridiagonal A.

Simon and Jacquez (1992), Hyman et al. (1999), McCluskey (2003), Guo and L. (2006, 2008), Gumel et al. (2006), Iggidr et al. (2007), Bame et al. (2008), Guo-Li-Shuai (2012), ...,

Results

Typical behaviours in epidemic models are convergence to equilibria.

Theorem (Guo-Li-Shuai (2012), Liu-Li (2018))

Under suitable assumptions of the nonlinear functions in the model,

(a) *If* $\mathcal{R}_0 \leq 1$, *then the disease-free equilibrium* $P_0 = (\bar{S}, 0, \cdots 0)$ *is globally stability in the feasible region* Γ.

(b) *If* $\mathcal{R}_0 > 1$, *then* P_0 *is unstable, and a unique endemic equilibrium* $P^* = (S^*, I_1^*, \cdots, I_n^*)$ *is globally stable in the interior of the feasible region* Γ.

$$\Gamma = \{(S, I_1, \cdots, I_n) \in \mathbb{R}^{n+1} \mid S + I_1 + \cdots + I_n \leq M\}.$$

Mathematical challenge is to show that:

- P^* is unique when $\mathcal{R}_0 > 1$, and
- P^* is stable and attracts points (GAS) in the interior of Γ.

Proof of GAS was done using a Lyapunov function - graph theoretic approach (Guo-Li-Shuai (2010)).

Question: Can the graph theoretic approach be extended to continuous state models?

Continuous State-Structured Model

Joint work with Drs. Zhipeng Qiu and Zhongwei Shen.

Let

- $S(t)$: number of susceptible individuals at time t
- $I(t,x)$: number of infected individuals at state x and time t
- $R(t)$: number of individuals recovered from infection at time t.

The model equation:

$$\dot{S}(t) = \Lambda(S(t)) - \int_\Omega f(y, S(t), I(t,y))dy,$$

$$I_t(t,x) = \alpha(x)\int_\Omega f(y, S(t), I(t,y))dy + \int_\Omega \theta(y,x)I(t,y)dy - \gamma(x)I(t,x) - \kappa(x)I(t,x) - \delta(x)I(t,x),$$

$$\dot{R}(t) = \int_\Omega \delta(x)I(t,x)dx - dR(t).$$

Reduced system:

$$\dot{S}(t) = \Lambda(S(t)) - \int_\Omega f(y, S(t), I(t,y))dy,$$

$$I_t(t,x) = \alpha(x)\int_\Omega f(y, S(t), I(t,y))dy + \int_\Omega \theta(y,x)I(t,y)dy - \gamma(x)I(t,x) - \kappa(x)I(t,x).$$

Denote $\mathbb{R}_+ = [0,\infty)$ and $\mathbb{R}_{++} = (0,\infty)$. Let $\Omega \subset \mathbb{R}^N$ be compact and connected with a smooth boundary and $\Omega = \mathrm{Cl}(\mathrm{int}(\Omega))$

Denote

$$C_+(\Omega) = \{h \in C(\Omega) \ : \ h \geq 0\}, \quad \text{and}$$
$$C_{++}(\Omega) = \{h \in C(\Omega \times \mathbb{R}_+) \ : \ \inf_{\Omega\times\mathbb{R}_+} h > 0\}.$$

Assumptions:

- $\Lambda \in C^1(\mathbb{R}_+, \mathbb{R})$, and $\exists$ a unique $S_0 > 0$ such that $\Lambda(S^0) = 0$ and $\Lambda(S) > 0$ for $0 < S < S_0$ and $\Lambda(S) < 0$ for $S > S_0$, and that $\Lambda'(S^0) < 0$.
- $f \in C(\Omega \times \mathbb{R}^2_+, \mathbb{R}) \cap C^1(\Omega \times \mathbb{R}^2_{++}, \mathbb{R})$ and satisfies the following properties:
  - $f(x, 0, I) = f(x, S, 0) = 0$ for all $(x, S, I) \in \Omega \times \mathbb{R}^2_+$;
  - for $x \in \Omega$ and $S > 0$, $f(x, S, I)$ is non-decreasing w.r.t $I \in \mathbb{R}_+$;
  - for $x \in \Omega$ and $I > 0$, $f(x, S, I)$ is increasing w.r.t. $S \in \mathbb{R}_+$;
  - for $x \in \Omega$ and $S \geq 0$, $\frac{f(x,S,I)}{I}$ is non-increasing w.r.t. $I \in \mathbb{R}_{++}$;
- $\kappa \in C_{++}(\Omega)$, and $\alpha \in C_+(\Omega)$ satisfies $\int_\Omega \alpha(x)dx = 1$;
- $\theta \in C(\Omega \times \Omega, \mathbb{R}_+)$ and satisfies $\theta(x, x) > 0$ for all $x \in \Omega$;
- $\gamma \in C_+(\Omega)$ satisfies the balance condition

$$\int_\Omega \theta(x, y)dy = \gamma(x), \quad \forall x \in \Omega.$$

Nonlinear Semigroup

Set $u(t) = (S(t), I(\cdot, t))^T$. Rewrite the system in the abstract form:

$$\dot{u}(t) = Au(t) + F(u(t)),$$

where operators A and F are defined as

$$A\begin{pmatrix} S \\ I \end{pmatrix} = \begin{pmatrix} \Lambda'(0)S \\ \int_\Omega \theta(y, \cdot)I(y)dy - \gamma I - \kappa I. \end{pmatrix}$$

and

$$F\begin{pmatrix} S \\ I \end{pmatrix} = \begin{pmatrix} \Lambda(S) - \Lambda'(0)S - \int_\Omega f(y, S, I(y))dy \\ \alpha \int_\Omega f(y, S, I(y))dy \end{pmatrix}.$$

in the Banach space $X = \mathbb{R} \times C(\Omega)$ equipped with the norm

$$\|(S, I)^T\|_X = |S| + \|I\|_{C(\Omega)} = |S| + \sup_{x \in \Omega} |I(x)|, \quad (S, I)^T \in X.$$

Let $X_+ := \mathbb{R}_+ \times C_+(\Omega)$ denote the closed positive cone of X and $X_{++} := \mathbb{R}_{++} \times C_{++}(\Omega)$ the interior of X_+.

Well-Posedness, Positivity and Dissipativity

Theorem (Qiu-Li-Shen, 2017)

For any $u_0 \in X_+$, there exists a unique global classical solution $u : [0, \infty) \to X_+$ with $u(0) = u_0$. Moreover, the semi-flow defined by

$$\Sigma(t)u_0 = u(t), \quad t \geq 0, \quad u_0 \in X_+$$

is bounded dissipative and asymptotically smooth, and hence, it admits a global attractor in X_+.

Challenges: Due to the integral form of the system, the semigroup lacks the usual regularity. The dissipativeness in X_+ is done by directly proving asymptotic smoothness.

Threshold Operator and $\mathcal{R}_0$

The threshold operator, $\mathcal{L} : C(\Omega) \to C(\Omega)$ is defined as

$$\mathcal{L}[I](x) = \frac{\alpha(x)}{\kappa(x)+\gamma(x)} \int_\Omega f_I(y, S^0, 0) I(y) dy + \frac{\int_\Omega \theta(y,x) I(y) dy}{\kappa(x)+\gamma(x)}, \quad x \in \Omega.$$

Proposition

- *The operator $\mathcal{L}$ is compact and non-supporting.*
- *The spectral radius $r(\mathcal{L})$ is a positive and algebraically simple eigenvalue of $\mathcal{L}$ with an eigenfunction in $C_{++}(\Omega)$.*
- *If λ is an eigenvalue of $\mathcal{L}$ with an eigenfunction in $C_+(\Omega) \setminus \{0\}$, then $\lambda = r(\mathcal{L})$.*

Define the basic reproduction number as:

$$\mathcal{R}_0 = r(\mathcal{L}).$$

$\mathcal{R}_0$ and Linear Stability

To relate $\mathcal{R}_0$ to linear stability of the disease-free equilibrium P_0, we examine the linearized equation at $P_0 = (S^0, 0)^T$:

$$\dot{S}(t) = \Lambda'(S^0)S(t) - \int_\Omega f_I(y, S^0, 0)I(t, y)dy,$$

$$I_t(t, x) = \alpha \int_\Omega f_I(y, S^0, 0)I(t, y)dy + \int_\Omega \theta(y, x)I(t, y)dy - (\gamma(x) + \kappa(x))I(x).$$

and the operators:

$$\begin{aligned} L[I](x) &= \alpha(x) \int_\Omega f_I(y, S^0, 0)I(y)dy + \int_\Omega \theta(y, x)I(y)dy - (\gamma(x) + \kappa(x))I(x) \\ &= U[I] + T[I] \end{aligned}$$

Let $s(L) := \sup\{\mathrm{Re}\lambda \ : \ \lambda \in \sigma(L)\}$ be the spectral bound of L

Theorem

1. *If* $s(L) > s(T)$, *then* $s(L)$ *is an isolated and simple eigenvalue of* L, *whose eigen-space is spanned by* $\phi \in C_{++}(\Omega)$, *and if* $\lambda \in \sigma(L)$ *and* $\lambda \neq s(L)$, *then* $Re\lambda < s(L)$.
2. *Conversely, if there exist* $\lambda_p \in \mathbb{R}$ *and* $\phi_p \in C_{++}(\Omega)$ *such that* $L\phi_p = \lambda_p \phi_p$, *then* $s(L) = \lambda_p > s(T)$.
3. *The disease-free equilibrium* $(S^0, 0)^T$ *is asymptotically stable if* $s(L) < 0$ *and unstable if* $s(L) > 0$.

Proposition

$s(L) > 0$, $s(L) = 0$ *and* $s(L) < 0$ *if and only if* $r(\mathcal{L}) > 1$, $r(\mathcal{L}) = 1$ *and* $r(\mathcal{L}) < 1$, *respectively.*

Theorem

The disease-free equilibrium $(S^0, 0)^T$ *is asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

Main Result

Theorem (Qiu-Li-Shen, 2017)

- *If* $\mathbb{R}_0 \leq 1$, *then the disease-free equilibrium* P_0 *is globally asymptotically stable in* X_+.
- *If* $\mathbb{R}_0 > 1$, *then* P_0 *is unstable and the model is uniformly persistent in* X_+.
- *If* $\mathbb{R}_0 > 1$, *then the model admits a positive stationary solution* $P^* = (S^*, I^*)^T$ *in* X_+ *with* $I^* \in C_{++}(\Omega)$.
- *If* $\mathbb{R}_0 > 1$, *and*

$$\left[\frac{S^*}{S} - \frac{f(x, S^*, I^*(x))}{f(x, S, I)}\right]\left[\frac{S^*}{S} - \frac{\frac{f(x,S^*,I^*(x))}{I^*(x)}}{\frac{f(x,S,I)}{I}}\right] \leq 0, \quad \forall x \in \Omega,\ S, I > 0,$$

then P^* *is globally asymptotically stable in* X_{++}. *In particular,* $(S^*, I^*)^T$ *is the unique endemic equilibrium.*

The Lyapunov Functional

Set $\phi(a) = a - 1 - \log a$. The proof uses a candidate Lyapunov functional of form

$$V(S(t), I(t,\cdot)) := \int_\Omega \eta(x)\left[\alpha(x)S^*\phi\left(\frac{S(t)}{S^*}\right) + I^*(x)\phi\left(\frac{I(t,x)}{I^*(x)}\right)\right]dx.$$

Need to choose a suitable function $\eta(x)$ so that $V(S(t), I(t,\cdot))$ is a Lyapunov functional!

While there is no longer a graph in the continuous case, the selection of $\eta(x)$ is guided by the same principle as in the discrete case: $\eta(x)$ is the eigenfunction of the Laplacian operator of certain linear operator with respect to the eigenvalue 0.

The Lyapunov Functional

Define a linear operator with kernel:

$$\mathcal{K}(x,y) := \theta(y,x)I^*(y) + \alpha(x)f(y,S^*,I^*(y)), \quad (x,y) \in \Omega \times \Omega.$$

Then $\mathcal{K} \in C(\Omega \times \Omega)$ and $\mathcal{K}(x,x) > 0$ for $x \in \Omega$, and there exists almost everywhere positive Borel function η on Ω such that (Thieme, 2011)

$$\int_\Omega \eta(x)\left(\int_\Omega \mathcal{K}(x,y)(v(x) - v(y))dy \right) dx = 0, \quad \forall v \in L^\infty(\Omega).$$

Compare to the discrete case:

$$\sum_i c_i \sum_j m_{ij}(G_i - G_j) = 0, \quad \text{for any } G_i,\ i = 1, \cdots, n$$

$(c_1, \cdots, c_n)^T$ is an eigenvector of the algebraic Laplacian matrix of a irreducible matrix (m_{ij}) with respect to eigenvalue 0.

Such a choice of $\eta(x)$ makes the Lyapunov functional work.

Summary

- For infectious diseases, states can be considered for susceptibility, infectivity, immunity, level of resistance, etc.
- Considering state structures can be fruitful from both mathematical and biological viewpoints.
- State-structured models, both discrete and continuous, give rise to considerable challenges in their analysis, stimulating development of mathematical theory.
  - Integral form leads to lack of regularity
  - Nonlocal terms due to switching of states cause problems in linear stability analysis and global stability analysis.
- Biologically, disease states are impacted by medical and pharmaceutical interventions. Investigations of how disease states change in response to current or potential treatments would provide insights to the development of treatments and vaccines.

Thank you!