

This notebook presents the analysis of the four models proposed in the manuscript. The models begin with the same essential structure: energy from the environment is assimilated at a rate Θ into a “bin” of energy E . This energy bin is the ultimate source of energy for all metabolic processes, including immune system proliferation and pathogen replication. The models differ in structure “downstream” of the E -bin. We propose four models:

- 1) Energy from the E -bin is allocated to two downstream energy bins, E_I and E_N , that serve as the energy sources for the immune system and pathogens, respectively. We call this model the *independent energy* model because the immune system and pathogens have separate resources that do not interact in any way.
- 2) Energy from the E -bin is allocated to a downstream E_I -bin used by the immune system, but the pathogen uses energy directly from the E -bin. We call this model the *pathogen priority* model because the pathogen is able to supercede immune allocation.
- 3) Energy from the E -bin is allocated to a downstream E_N -bin used by pathogens, but the immune system uses energy directly from the E -bin. We call this model the *immune priority* model, as it is the opposite of pathogen priority model.
- 4) Immune proliferation and pathogen replication both require energy from the E -bin. We call this model the *energy antagonism* model because the immune system and pathogens are competing for the same resource.

Below we analyze each model, focusing on how equilibrium pathogen load and number of immune cells change with increasing the energy assimilation rate Θ .

Independent energy model

In the independent energy model, the E -bin is used to fuel non-epidemiological processes at a per-capita rate r and flows to two downstream energy bins, E_I and E_N , used by the immune system and pathogen, respectively, at rates r_I and r_N . The host is assumed to use the energy in the E_N -bin for its own metabolic purposes at a per-capita rate a . All other epidemiological processes occur as in the energy antagonism model, with E_I and E_N bins replacing the E bin.

$$\begin{aligned} \frac{dE}{dt} &= \Theta - rE - r_I E - r_N E; \\ \frac{dE_I}{dt} &= r_I E - a_B E_I - a_I f_I E_I I; \\ \frac{dE_N}{dt} &= r_N E - a E_N - f_N E_N N; \\ \frac{dI}{dt} &= \frac{a_B E_I + a_I f_I E_I I}{\epsilon_I} - m I; \\ \frac{dN}{dt} &= \frac{f_N E_N N}{\epsilon_N} - f_I I N - d N; \end{aligned}$$

It is easier for the analysis to use a nondimensionalized version of this model. Nondimensionalize by letting $\tau = rt$, $e = a_I E / \epsilon_N$, $e_i = a_I E_I / \epsilon_N$, $e_n = a_I E_N / \epsilon_N$, $i = a_I \epsilon_I I / \epsilon_N$, and $n = a_I N$ and $\theta = \frac{a_I \Theta}{r \epsilon_N}$, $\rho_i = r_I / r$, $\rho_n = r_N / r$, $\alpha_i = a_B / r$,

$$\alpha_n = a / r, \quad \phi = \frac{f_I \epsilon_N}{a_I r \epsilon_I}, \quad \sigma = \frac{f_N}{a_I r}, \quad \mu = m / r, \quad \text{and } \delta = d / r.$$

$$\begin{aligned} \frac{de}{d\tau} &= \theta - e - \rho_i e - \rho_n e; \\ \frac{de_i}{d\tau} &= \rho_i e - \alpha_i e_i - \phi e_i i; \\ \frac{di}{d\tau} &= \alpha_i e_i + \phi e_i i - \mu i; \\ \frac{de_n}{d\tau} &= \rho_n e - \alpha_n e_n - \sigma e_n n; \\ \frac{dn}{d\tau} &= \sigma e_n n - \phi i n - \delta n; \end{aligned}$$

The equilibria of this system are:

```

equils =
Solve[{dedt == 0, deidt == 0, didt == 0, dendt == 0, dndt == 0}, {e, ei, i, en, n}]
{ { e -> \frac{\theta}{1 + \rho i + \rho n}, ei -> (\theta \mu \rho i \sigma (\delta \mu + \delta \mu \rho i + \delta \mu \rho n + \theta \rho i \phi)) /
(\alpha i \delta \mu^2 \sigma + 2 \alpha i \delta \mu^2 \rho i \sigma + \alpha i \delta \mu^2 \rho i^2 \sigma + 2 \alpha i \delta \mu^2 \rho n \sigma + 2 \alpha i \delta \mu^2 \rho i \rho n \sigma +
\alpha i \delta \mu^2 \rho n^2 \sigma - \alpha n \delta \theta \mu \rho i \phi - \alpha n \delta \theta \mu \rho i^2 \phi - \alpha n \delta \theta \mu \rho i \rho n \phi + \alpha i \theta \mu \rho i \sigma \phi +
\alpha i \theta \mu \rho i^2 \sigma \phi + \alpha i \theta \mu \rho i \rho n \sigma \phi + \theta^2 \mu \rho i \rho n \sigma \phi - \alpha n \theta^2 \rho i^2 \phi^2),
i -> \frac{\theta \rho i}{\mu (1 + \rho i + \rho n)}, en -> \frac{\delta \mu + \delta \mu \rho i + \delta \mu \rho n + \theta \rho i \phi}{\mu (1 + \rho i + \rho n) \sigma},
n -> \frac{-\alpha n \delta \mu - \alpha n \delta \mu \rho i - \alpha n \delta \mu \rho n + \theta \mu \rho n \sigma - \alpha n \theta \rho i \phi}{\sigma (\delta \mu + \delta \mu \rho i + \delta \mu \rho n + \theta \rho i \phi)} },
{ { e -> \frac{\theta}{1 + \rho i + \rho n}, ei -> \frac{\theta \rho i}{\alpha i (1 + \rho i + \rho n)}, i -> \frac{\theta \rho i}{\mu (1 + \rho i + \rho n)},
en -> \frac{\theta \rho n}{\alpha n (1 + \rho i + \rho n)}, n -> 0 } }

```

We will again analyze the response of the equilibrium immune abundance i and pathogen load n to changes in energy assimilation θ (that is, $i'(\theta)$ and $n'(\theta)$). It is actually quite straightforward to show that **both equilibrium immune abundance and equilibrium pathogen load are strictly increasing functions of θ** .

```

iequil = equils[[1, 3, 2]];
nequil = equils[[1, 5, 2]];
D[iequil, \theta]
Simplify[D[nequil, \theta]]

```

$$\frac{\rho i}{\mu (1 + \rho i + \rho n)}$$

$$\frac{\delta \mu^2 \rho n (1 + \rho i + \rho n)}{(\delta \mu (1 + \rho i + \rho n) + \theta \rho i \phi)^2}$$

Pathogen priority model

In the pathogen priority model, the E -bin fuels non-epidemiological processes at a per-capita rate r . Energy flows to a downstream bin E_I at a per-capita rate r_I . Energy in the E_I -bin is used by the immune system to fuel immune proliferation. The pathogen steals energy directly from the E -bin. All other epidemiological processes occur as in the energy antagonism model, with E_I replacing E in the immune equations.

```

dEdt = \theta - r E - r I E - f N E N;
dEIdt = r I E - a B E I - a I f I E I I N;
dIdt = \frac{a B E I + a I f I E I I N}{\epsilon I} - m I;
dNdt = \frac{f N E N}{\epsilon N} - f I I N - d N;

```

It is easier for the analysis to use a nondimensionalized version of this model. Nondimensionalize by letting $\tau=rt$, $e = a_I E/\epsilon_N$, $e_i = a_I E_I/\epsilon_N$, $i = a_I \epsilon_I I/\epsilon_N$, and $n = a_I N$ and $\theta = \frac{a_I \theta}{r \epsilon_N}$, $\rho_i = r_I/r$, $\alpha_i = a_B/r$, $\phi = \frac{f_I \epsilon_N}{a_I r \epsilon_I}$, $\sigma = \frac{f_N}{a_I r}$, $\mu = m/r$, and δ

$= d/r.$

```
dedt =  $\theta - e - \rho i e - \sigma e n$ ;
deidt =  $\rho i e - \alpha i e i - \phi e i i n$ ;
didt =  $\alpha i e i + \phi e i i n - \mu i$ ;
dndt =  $\sigma e n - \phi i n - \delta n$ ;
```

The equilibria of this system are:

```
equils = Solve[{dedt == 0, deidt == 0, didt == 0, dndt == 0}, {e, ei, i, n}]
```

$$\left\{ \left\{ e \rightarrow \frac{\delta \mu}{\mu \sigma - \rho i \phi}, \right. \right. \\ \left. \left. \begin{aligned} ei \rightarrow -(\delta \mu^2 \rho i \sigma) / (-\alpha i \mu^2 \sigma^2 + \delta \mu \rho i \phi + \delta \mu \rho i^2 \phi + \alpha i \mu \rho i \sigma \phi - \theta \mu \rho i \sigma \phi + \theta \rho i^2 \phi^2), \\ i \rightarrow -\frac{\delta \rho i}{-\mu \sigma + \rho i \phi}, n \rightarrow \frac{-\delta \mu - \delta \mu \rho i + \theta \mu \sigma - \theta \rho i \phi}{\delta \mu \sigma} \end{aligned} \right\}, \right. \\ \left. \left\{ e \rightarrow \frac{\theta}{1 + \rho i}, ei \rightarrow \frac{\theta \rho i}{\alpha i (1 + \rho i)}, i \rightarrow \frac{\theta \rho i}{\mu (1 + \rho i)}, n \rightarrow 0 \right\} \right\}$$

The signs of $i'(\theta)$ and $n'(\theta)$ are given by the derivatives:

```
iequil = equils[[1, 3, 2]];
nequil = equils[[1, 4, 2]];
D[iequil,  $\theta$ ]
D[nequil,  $\theta$ ]
```

0

$$\frac{\mu \sigma - \rho i \phi}{\delta \mu \sigma}$$

Clearly, **equilibrium immune abundance i is independent of θ** . This can be seen by writing the immune equilibrium in terms of e only, and noting that the equilibrium e is independent of θ .

```
Solve[dndt == 0, i]
```

$$\left\{ \left\{ i \rightarrow \frac{-\delta + e \sigma}{\phi} \right\} \right\}$$

To determine whether the pathogen load increases or decreases, we need to know the sign of $\mu \sigma - \rho i \phi$. The pathogen can only successfully colonize the host when the pathogen-free equilibrium is unstable, that is, when

$$-\delta + \frac{\theta \sigma}{1 + \rho i} - \frac{\theta \rho i \phi}{\mu (1 + \rho i)} > 0.$$

```
Eigenvalues[{D[dedt, e], D[dedt, ei], D[dedt, i], D[dedt, n]},
  {D[deidt, e], D[deidt, ei], D[deidt, i], D[deidt, n]},
  {D[didt, e], D[didt, ei], D[didt, i], D[didt, n]},
  {D[dndt, e], D[dndt, ei], D[dndt, i], D[dndt, n]}] /. equils[[2]]
```

$$\left\{ -\alpha i, -\mu, -1 - \rho i, -\delta + \frac{\theta \sigma}{1 + \rho i} - \frac{\theta \rho i \phi}{\mu (1 + \rho i)} \right\}$$

But this condition implies that $\frac{\theta \sigma}{1 + \rho i} - \frac{\theta \rho i \phi}{\mu (1 + \rho i)} > 0 \implies \sigma \mu - \rho i \phi > 0$. Thus we know that **equilibrium pathogen load n is a strictly increasing function of θ** . This makes sense: pathogen energy theft preempts energy allocation to the immune bin, so increasing energy assimilation only benefits the pathogen - the extra energy is essentially completed used up by the pathogen.

Immune priority model

In the immune priority model, the E -bin fuels non-epidemiological processes at a per-capita rate r . Energy flows to a downstream bin E_N at a per-capita rate r_N . Energy in the E_N -bin is used by the host at a per-capita rate a and is stolen by the pathogen at the per-pathogen rate f_N . Immune proliferation is fuelled with energy from the E -bin. All other epidemiological processes occur as in the energy antagonism model, with E_N replacing E in the pathogen equations.

$$dEdt = \Theta - r E - a B E - a I f I E I N - r N E;$$

$$dENDt = r N E - a E N - f N E N N;$$

$$dIdt = \frac{a B E + a I f I E I N}{e I} - m I;$$

$$dNdt = \frac{f N E N N}{e N} - f I I N - d N;$$

$$\text{Solve}[dENDt == 0, N]$$

$$\left\{ \left\{ N \rightarrow \frac{-a E N + r n E}{E N f n} \right\} \right\}$$

$$\text{Solve}[dENDt == 0, EN]$$

$$\left\{ \left\{ EN \rightarrow \frac{r n E}{a + f n N} \right\} \right\}$$

$$\text{Solve}[dEdt == 0, I]$$

$$\left\{ \left\{ I \rightarrow \frac{-a b E - r E - r n E + \Theta}{a i f i E N} \right\} \right\}$$

It is easier for the analysis to use a nondimensionalized version of this model. Nondimensionalize by letting $\tau=rt$, $e = a_I E/\epsilon_N$, $e_i = a_I E_I/\epsilon_N$, $e_n = a_I E_N/\epsilon_N$, $i = a_I \epsilon_I I/\epsilon_N$, and $n = a_I N$ and $\theta = \frac{a_I \Theta}{r \epsilon_N}$, $\rho_i = r_I/r$, $\rho_n = r_N/r$, $\alpha_i = a_B/r$, $\alpha_n = a/r$, $\phi = \frac{f_I \epsilon_N}{a_I r \epsilon_I}$, $\sigma = \frac{f_N}{a_I r}$, $\mu = m/r$, and $\delta = d/r$. We make the implicit dependence of the state variables on θ explicit here.

$$dedt = \theta - e[\theta] - \rho_n e[\theta] - \alpha_i e[\theta] - \phi e[\theta] i[\theta] n[\theta];$$

$$dendt = \rho_n e[\theta] - \alpha_n e n[\theta] - \sigma e n[\theta] n[\theta];$$

$$didt = \alpha_i e[\theta] + \phi e[\theta] i[\theta] n[\theta] - \mu i[\theta];$$

$$\text{percapdndt} = \sigma e n[\theta] - \phi i[\theta] - \delta;$$

$$\text{Solve}[didt == 0, n[\theta]]$$

$$\left\{ \left\{ n[\theta] \rightarrow \frac{-\alpha_i e[\theta] + \mu i[\theta]}{\phi e[\theta] i[\theta]} \right\} \right\}$$

We then set each equation equal to zero and implicitly differentiate to get implicit equation for the derivatives of the state variables as a function of energy assimilation θ .

$$\text{ImplicitDerivs} = \text{FullSimplify}[$$

$$\text{Solve}[\text{Simplify}[D[\{dedt == 0, dendt == 0, didt == 0, percapdndt == 0\}, \theta]],$$

$$\{e'[\theta], en'[\theta], i'[\theta], n'[\theta]\}];$$

We show below that: **equilibrium immune abundance is a strictly increasing function of energy assimilation θ , whereas equilibrium pathogen load peaks at an intermediate value of energy assimilation θ .**

■ Determining the response of immune abundance to changes in θ

The equation for $i'(\theta)$ is:

```

iprime = ImplicitDerivs[[1, 3, 2]] /. {e[θ] → e, i[θ] → i, n[θ] → n, en[θ] → en}
(σ (e i ρ n φ + en σ (α i + i n φ))) / (e i φ (μ ρ n σ + α n (1 + ρ n) φ + n (1 + ρ n) σ φ) +
en σ2 (-e n (1 + ρ n) φ + μ (1 + α i + ρ n + i n φ)))

```

Nearly every term in this derivative is positive. The expression in the denominator involving negative terms can be simplified so that if we can show that $\mu - \phi e n > 0$, we will have proven that the derivative is positive.

```

(-e n (1 + ρ n) φ + μ (1 + α i + ρ n + i n φ)) == (1 + ρ n) (μ - φ e n) + α i μ + i n μ φ // Simplify
True

```

We can prove this inequality by noting that, at equilibrium, $\alpha_i e + \phi e i n = \mu i$ (from solving $di/dt=0$). This implies that $\mu i > \phi e i n \Rightarrow \mu - \phi e n > 0$. So we have shown that **the equilibrium immune abundance is a strictly increasing function of energy assimilation θ** .

■ Determining the response of pathogen load to changes in θ

Turning our attention to $n'(\theta)$, we begin by noting the the denominator of $n'(\theta)$ is identical to the denominator of $i'(\theta)$. Since we have already shown that the denominator of $i'(\theta)$ was positive, we can focus our attention on the numerator only.

```

nprime = ImplicitDerivs[[1, 4, 2]] /. {e[θ] → e, i[θ] → i, n[θ] → n, en[θ] → en};
Denominator[nprime] == Denominator[nprime]
Expand[Numerator[nprime]]
True

```

$$\mu \rho n \sigma - \alpha_i \alpha_n \phi - n \alpha_i \sigma \phi - e n \rho n \sigma \phi - i n \alpha_n \phi^2 - i n^2 \sigma \phi^2$$

The numerator has a single positive term, followed by several negative terms that involve the state variables. I have already shown that equilibrium immune abundance i is an increasing function of θ . It is straightforward to show that equilibrium energy level is also a strictly increasing function of θ by noting that the denominators of $e'(\theta)$ and $i'(\theta)$ are identical and that the only expression in the numerator that involves a negative sign ($\mu - \phi e n$) has already been shown above to always be positive.

```

eprime = ImplicitDerivs[[1, 1, 2]] /. {e[θ] → e, i[θ] → i, n[θ] → n, en[θ] → en};
Denominator[eprime] == Denominator[iprime]
Numerator[eprime]
True

```

$$e i (\alpha n + n \sigma) \phi^2 + e n \sigma^2 (\mu - e n \phi)$$

This analysis suggests that $n'(\theta)$ likely *becomes* negative as θ increases (a fixed positive term minus several increasing negative terms). I can show that $n'(\theta)$ is positive for small values of θ by considering the value at the point where the pathogen is just able to colonize the host - that is, calculate the value of $n'(\theta)$ at the pathogen-free equilibrium.

```

pathfreeequil =
Solve[{dedt == 0, dendt == 0, didt == 0} /. {n[θ] → 0}, {e[θ], en[θ], i[θ]}}][[1]] /.
{e[θ] → e, en[θ] → en, i[θ] → i}
Simplify[nprime /. {n → 0} /. pathfreeequil]

```

$$\left\{ e \rightarrow \frac{\theta}{1 + \alpha i + \rho n}, \text{ en} \rightarrow \frac{\theta \rho n}{\alpha n (1 + \alpha i + \rho n)}, i \rightarrow \frac{\alpha i \theta}{\mu (1 + \alpha i + \rho n)} \right\}$$

$$\frac{\mu \rho n \sigma - \alpha_i \alpha_n \phi}{\alpha n} + \frac{\alpha_i \theta^2 \phi (\mu \rho n \sigma + \alpha n (1 + \rho n) \phi)}{\mu (1 + \alpha i + \rho n)^2}$$

The sign of $n'(\theta)$ is determined by the sign of $\mu \rho_n \sigma - \alpha_i \alpha_n \phi$. However, for the pathogen to be able to invade, its per-capita growth rate, when the host is its the pathogen-free equilibrium, must be positive. In order for this to be true, μ

$\rho_n \sigma - \alpha_i \alpha_n \phi$ must be positive, as can be seen below.

```
(percapdndt /. {e[θ] → e, en[θ] → en, i[θ] → i} /. pathfreeequil) ==
  (μ ρn σ - αi αn φ)
  -----
  αn μ (1 + αi + ρn) - δ // Simplify
```

True

So $n'(\theta)$ is **positive at the lower boundary of pathogen persistence**. This only strengthens the conviction that $n'(\theta)$ must become negative at some point, because if it were to remain positive, the sign determining expression would be a single positive term minus several terms, all of which are increasing in magnitude. The only way this would be possible is if the state variables only increased to some asymptote that was much smaller than $\mu \rho_n \sigma$.

We will prove that $n'(\theta)$ must become negative by contradiction. That is, we will assume that $n'(\theta)$ is strictly increasing and then show that leads to a logical fallacy.

We do this by using implicit differentiation to calculate the second derivative $i''(\theta)$.

```
ImplicitSecondDerivs = FullSimplify[
  Solve[Simplify[D[{dedt == 0, dendt == 0, didt == 0, percapdndt == 0}, {θ, 2}],
    {e''[θ], en''[θ], i''[θ], n''[θ]}]] /.
  {e[θ] → e, en[θ] → en, i[θ] → i, n[θ] → n};
i2prime = ImplicitSecondDerivs[[1, 3, 2]]
(2 (1 + ρn) σ² φ (en n e'[θ] i'[θ] + (-e i en'[θ] + en (i e'[θ] + e i'[θ])) n'[θ])) /
(e i φ (μ ρn σ + αn (1 + ρn) φ + n (1 + ρn) σ φ) +
en σ² (-e n (1 + ρn) φ + μ (1 + αi + ρn + i n φ)))
```

The denominator is guaranteed to be positive (it is identical to the denominators in the first derivative terms above), so we can focus again on the numerator only. Given that we have already shown that $e'(\theta)$ and $i'(\theta)$ are strictly positive, and we are assuming that $n'(\theta)$ is also strictly positive, the only expression that might be negative is $(-e i en'[\theta] + en (i e'[\theta] + e i'[\theta]))$. Plugging the equations for $e'(\theta)$, $i'(\theta)$, and $e_n'(\theta)$ into this expression, we get:

```
ex = Simplify[(-e i en'[θ] + en (i e'[θ] + e i'[θ])) /. ImplicitDerivs[[1]] /.
  {e[θ] → e, en[θ] → en, i[θ] → i, n[θ] → n}
(en² i μ σ² + e² i ρn φ (en σ - i φ) + e en (en αi σ² + i φ (-αi σ + i αn φ))) /
(e i φ (μ ρn σ + (1 + ρn) (αn + n σ) φ) + en σ² (-e n (1 + ρn) φ + μ (1 + αi + ρn + i n φ)))
```

The denominator is strictly positive. The numerator is also strictly positive, which can be seen by rewriting it as:

```
Numerator[ex] == (e en αi σ + e² i ρn φ) (σ en - φ i) + e en i² αn φ² + en² i μ σ² // Simplify
```

True

This proves that $i''(\theta)$ is strictly positive. Since $i'(\theta)$ is positive, the implication is that i never asymptotes, meaning that as $\theta \rightarrow \infty$, $i \rightarrow \infty$. Recalling the sign-determining expression for $n'(\theta)$, this proves that our assumption that $n'(\theta)$ is strictly positive cannot be true: if $n'(\theta)$ is strictly positive, then $i(\theta)$ approaches infinity as θ is increased, leading to the sign-determining numerator of $n'(\theta)$ to become negative.

```
Expand[Numerator[nprime]]
```

```
μ ρn σ - αi αn φ - n αi σ φ - e n ρn σ φ - i n αn φ² - i n² σ φ²
```

By contradiction, $n'(\theta)$ cannot be strictly increasing, and must become negative as θ increases. This implies that there is a value of θ that leads to an intermediate peak in pathogen load n .

Energy antagonism model

In the energy antagonism model, energy is assimilated into the E -bin at a rate Θ and is used to fuel all non-epidemiological metabolic processes at a constant per-capita rate r . Energy is allocated to the immune system at a constant per-capita rate a_B in the absence of infection. Contacts between immune cells I and pathogens N occur at the rate of f_I per immune cell and result in the killing of the pathogen. These contacts also increase the amount of energy allocated to the immune system by a factor of a_I per pathogen. The pathogen “steals” energy at a rate f_N to fuel its own replication. Production of new immune cells or pathogens carries an energetic cost of ϵ_I and ϵ_N , respectively, and immune cells and pathogens die at a per-capita background mortality rate of m and d , respectively.

$$\frac{dE}{dt} = \Theta - rE - a_B E - a_I f_I E I N - f_N E N;$$

$$\frac{dI}{dt} = \frac{a_B E + a_I f_I E I N}{\epsilon_I} - m I;$$

$$\frac{dN}{dt} = \frac{f_N E N}{\epsilon_N} - f_I I N - d N;$$

It is easier for the analysis to use a non-dimensionalized version of this model. Nondimensionalize by letting $\tau = rt$, $e = a_I E / \epsilon_N$, $i = a_I \epsilon_I I / \epsilon_N$, and $n = a_I N$ and $\theta = \frac{a_I \Theta}{r \epsilon_N}$, $\alpha_i = a_B / r$, $\phi = \frac{f_I \epsilon_N}{a_I r \epsilon_I}$, $\sigma = \frac{f_N}{a_I r}$, $\mu = m / r$, and $\delta = d / r$.

$$\frac{de}{d\tau} = \theta - e - \alpha_i e - \phi e i n - \sigma e n;$$

$$\frac{di}{d\tau} = \alpha_i e + \phi e i n - \mu i;$$

$$\frac{dn}{d\tau} = \sigma e n - \phi i n - \delta n;$$

The equilibria of this system are given by solving

$$\text{equils} = \text{Simplify}[\text{Solve}[\{\text{dedt} == 0, \text{didt} == 0, \text{dndt} == 0\}, \{e, i, n\}]]$$

$$\left\{ \left\{ e \rightarrow \frac{\theta}{1 + \alpha_i}, i \rightarrow \frac{\alpha_i \theta}{\mu + \alpha_i \mu}, n \rightarrow 0 \right\}, \left\{ e \rightarrow \frac{1}{2 \sigma (\mu \sigma + \phi)} \left(2 \delta \mu \sigma - \mu \sigma^2 + \delta \phi + \alpha_i \sigma \phi + \theta \sigma \phi - \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right), \right. \right.$$

$$i \rightarrow -\frac{1}{2 \phi (\mu \sigma + \phi)} \left(\mu \sigma^2 + \delta \phi - \alpha_i \sigma \phi - \theta \sigma \phi + \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right),$$

$$n \rightarrow \left(\delta \mu^2 \sigma^2 - \delta^2 \mu \phi + 2 \delta \mu \sigma \phi + \alpha_i \delta \mu \sigma \phi + \delta \theta \mu \sigma \phi - \theta \mu \sigma^2 \phi - \delta \theta \phi^2 + \alpha_i \theta \sigma \phi^2 + \theta^2 \sigma \phi^2 + \delta \mu \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} + \theta \phi \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right) /$$

$$\left. \left(2 \delta \sigma \phi (\delta \mu - \mu \sigma + \theta \phi) \right) \right\}, \left\{ e \rightarrow \frac{1}{2 \sigma (\mu \sigma + \phi)} \left(2 \delta \mu \sigma - \mu \sigma^2 + \delta \phi + \alpha_i \sigma \phi + \theta \sigma \phi + \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right), \right.$$

$$i \rightarrow \frac{1}{2 \phi (\mu \sigma + \phi)} \left(-\mu \sigma^2 - \delta \phi + \alpha_i \sigma \phi + \theta \sigma \phi + \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right),$$

$$n \rightarrow \left(\delta \mu^2 \sigma^2 - \delta^2 \mu \phi + 2 \delta \mu \sigma \phi + \alpha_i \delta \mu \sigma \phi + \delta \theta \mu \sigma \phi - \theta \mu \sigma^2 \phi - \delta \theta \phi^2 + \alpha_i \theta \sigma \phi^2 + \theta^2 \sigma \phi^2 - \delta \mu \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} - \theta \phi \sqrt{(-4 \delta \sigma (\mu \sigma + \phi) (\delta \mu - \mu \sigma + \theta \phi) + (\delta (2 \mu \sigma + \phi) + \sigma (-\mu \sigma + (\alpha_i + \theta) \phi))^2)} \right) /$$

$$\left. \left(2 \delta \sigma \phi (\delta \mu - \mu \sigma + \theta \phi) \right) \right\} \}$$

The first equilibrium is the pathogen-extinction equilibrium. The second and third are conjugates of one another, but

only the third is feasible - the second gives rise to negative values for immune abundance. This can be seen by rewriting the immune equilibrium in the following way:

$$\text{equils}[[2, 2, 2]] == -\frac{1}{2\phi(\mu\sigma + \phi)} \left(\mu\sigma^2 + \delta\phi - \alpha i\sigma\phi - \theta\sigma\phi + \sqrt{(\mu\sigma^2 + \delta\phi - \alpha i\sigma\phi - \theta\sigma\phi)^2 + 4\alpha i\delta\sigma\phi(\mu\sigma + \phi)} \right) // \text{Simplify}$$

True

If $\mu\sigma^2 + \delta\phi - \alpha i\sigma\phi - \theta\sigma\phi > 0$, then the entire term in parentheses is obviously positive, and thus the equilibrium is negative. If $\mu\sigma^2 + \delta\phi - \alpha i\sigma\phi - \theta\sigma\phi < 0$, the square root term is still positive and is guaranteed to be larger than $\mu\sigma^2 + \delta\phi - \alpha i\sigma\phi - \theta\sigma\phi$, so the entire term in parentheses is positive, and thus the equilibrium is negative. A similar argument can be used to show that the third immune equilibrium is guaranteed to be positive.

We therefore focus on the third equilibrium only in the subsequent analysis. In particular, we analyze how equilibrium immune abundance and pathogen load change as the energy assimilation rate θ is increased. **We show that equilibrium immune abundance is a strictly increasing function of θ , whereas equilibrium pathogen load peaks at an intermediate value of θ .**

```
eequil = equils[[3, 1, 2]];
iequil = equils[[3, 2, 2]];
nequil = equils[[3, 3, 2]];

```

■ Determining the response of immune abundance to changes in θ

The derivative of the i equilibrium with respect to θ can be written as:

$$\text{Simplify}[D[\text{iequil}, \theta]] == \frac{\sigma}{2(\mu\sigma + \phi)} \left(1 + \frac{-\mu\sigma^2 - (\delta - (\alpha i + \theta)\sigma)\phi}{\sqrt{(-\mu\sigma^2 - (\delta - (\alpha i + \theta)\sigma)\phi)^2 + 4\alpha i\delta\sigma\phi(\mu\sigma + \phi)}} \right) // \text{Simplify}$$

True

If $-\mu\sigma^2 - (\delta - (\alpha i + \theta)\sigma)\phi > 0$, then the entire derivative is obviously positive. If $-\mu\sigma^2 - (\delta - (\alpha i + \theta)\sigma)\phi < 0$, the term in the denominator will still have greater magnitude, so the entire fraction will be less than 1, and the term in parentheses is thus guaranteed positive. **Therefore, the i equilibrium is a strictly increasing function of θ .**

■ Determining the response of pathogen load to changes in θ

It is simple to show that there is a θ value that causes a peak in the pathogen load.

Solve[D[nequil, θ] == 0, θ]

$$\left\{ \left\{ \theta \rightarrow \frac{1}{-\mu \sigma^2 \phi^2 + \alpha i \sigma \phi^3} \left(-\mu^2 \sigma^3 \phi - \delta \mu \sigma \phi^2 - \alpha i \delta \mu \sigma \phi^2 + \alpha i \mu \sigma^2 \phi^2 - \sqrt{\left(\alpha i \delta^2 \mu^3 \sigma^3 \phi^3 - 2 \alpha i \delta \mu^3 \sigma^4 \phi^3 + \alpha i \mu^3 \sigma^5 \phi^3 + 2 \alpha i \delta^2 \mu^2 \sigma^2 \phi^4 - 2 \alpha i \delta \mu^2 \sigma^3 \phi^4 + 2 \alpha i^2 \delta \mu^2 \sigma^3 \phi^4 - 2 \alpha i^2 \mu^2 \sigma^4 \phi^4 + \alpha i \delta^2 \mu \sigma \phi^5 + 2 \alpha i^2 \delta \mu \sigma^2 \phi^5 + \alpha i^3 \mu \sigma^3 \phi^5 \right)} \right) \right\}, \right. \\ \left. \left\{ \theta \rightarrow \frac{1}{-\mu \sigma^2 \phi^2 + \alpha i \sigma \phi^3} \left(-\mu^2 \sigma^3 \phi - \delta \mu \sigma \phi^2 - \alpha i \delta \mu \sigma \phi^2 + \alpha i \mu \sigma^2 \phi^2 + \sqrt{\left(\alpha i \delta^2 \mu^3 \sigma^3 \phi^3 - 2 \alpha i \delta \mu^3 \sigma^4 \phi^3 + \alpha i \mu^3 \sigma^5 \phi^3 + 2 \alpha i \delta^2 \mu^2 \sigma^2 \phi^4 - 2 \alpha i \delta \mu^2 \sigma^3 \phi^4 + 2 \alpha i^2 \delta \mu^2 \sigma^3 \phi^4 - 2 \alpha i^2 \mu^2 \sigma^4 \phi^4 + \alpha i \delta^2 \mu \sigma \phi^5 + 2 \alpha i^2 \delta \mu \sigma^2 \phi^5 + \alpha i^3 \mu \sigma^3 \phi^5 \right)} \right) \right\} \right\}$$

However, proving that one of these two θ values is both positive and large enough to permit the pathogen to colonize the host is somewhat trickier. We take a slightly roundabout approach the problem. We begin by rewriting the equilibrium pathogen load in terms of n only.

nequil2 = Solve[(didt /. Solve[dndt == 0, i][[1]]) == 0, n]

$$\left\{ \left\{ n \rightarrow \frac{-\delta \mu + e \mu \sigma - e \alpha i \phi}{e (-\delta + e \sigma) \phi} \right\} \right\}$$

Recognizing that the equilibrium n and e are both implicit function of θ , we can implicitly differentiate the equilibrium condition to calculate $n'(\theta)$:

Simplify[D[nequil2 /. {n -> n[θ], e -> e[θ]}, θ]

$$\left\{ \left\{ n'[\theta] \rightarrow \frac{(-\delta^2 \mu + 2 \delta \mu \sigma e[\theta] + \sigma (-\mu \sigma + \alpha i \phi) e[\theta]^2) e'[\theta]}{\phi e[\theta]^2 (\delta - \sigma e[\theta])^2} \right\} \right\}$$

The derivative of e with respect to θ is guaranteed to be positive. This can be seen by noting that $e'(\theta)$ is a constant positive multiple of $i'(\theta)$:

D[eequil, θ] / D[iequil, θ]

$$\frac{\phi}{\sigma}$$

Based on this analysis, it is clear that the sign and zeros of $n'(\theta)$ can be determined by looking at the sign and zeros of $n'(e)$. That is, because e is a function of θ , any value of e that satisfies $n'(e) = 0$ implies the existence of a θ value that satisfies $n'(\theta) = 0$ - an intermediate peak. Moreover, it is clear that such an e will make the term in parentheses in the numerator equal to zero. There are two possible e values that give rise to intermediate peaks in n :

epeak = Solve[- $\delta^2 \mu + 2 \delta \mu \sigma e[\theta] + \sigma (-\mu \sigma + \alpha i \phi) e[\theta]^2 == 0, e[\theta]$]

$$\left\{ \left\{ e[\theta] \rightarrow \frac{-\delta \mu \sigma - \sqrt{\alpha i} \delta \sqrt{\mu} \sqrt{\sigma} \sqrt{\phi}}{-\mu \sigma^2 + \alpha i \sigma \phi} \right\}, \left\{ e[\theta] \rightarrow \frac{-\delta \mu \sigma + \sqrt{\alpha i} \delta \sqrt{\mu} \sqrt{\sigma} \sqrt{\phi}}{-\mu \sigma^2 + \alpha i \sigma \phi} \right\} \right\}$$

Only one of these is actually feasible, however. To understand why, it is necessary to consider the conditions required for the pathogen to actually be able to persist. Mathematically, this corresponds to the conditions for instability of the pathogen-free equilibrium.

`equils[[1]] (* the pathogen-free equilibrium *)`

`Eigenvalues[`

`{D[dedt, e], D[dedt, i], D[dedt, n]}, {D[didt, e], D[didt, i], D[didt, n]},`
`{D[dndt, e], D[dndt, i], D[dndt, n]}} /. equils[[1]]`

$$\left\{ e \rightarrow \frac{\theta}{1 + \alpha i}, i \rightarrow \frac{\alpha i \theta}{\mu + \alpha i \mu}, n \rightarrow 0 \right\}$$

$$\left\{ -1 - \alpha i, -\mu, -\delta + \frac{\theta \sigma}{1 + \alpha i} - \frac{\alpha i \theta \phi}{\mu + \alpha i \mu} \right\}$$

Because the first two eigenvalues are negative, the pathogen - free equilibrium will be unstable if

$\frac{\theta \sigma}{1 + \alpha i} - \delta - \frac{\alpha i \theta \phi}{\mu + \alpha i \mu} > 0$. This condition can be understood intuitively as the per-capita growth rate of the pathogen when the host's energy and immune abundance are at their pathogen-free equilibria. This condition can be rewritten as $\sigma e - \delta - \phi i > 0$, or equivalently, as $\sigma e - \delta - \phi \alpha_i e / \mu > 0$. So, for pathogen invasion to occur, $e > \frac{\delta \mu}{\mu \sigma - \alpha_i \phi}$. We can show that the first candidate peak e satisfies this condition, but the second does not.

$$\text{Simplify}\left[\text{epeak}[[1, 1, 2]] > \frac{\delta \mu}{\mu \sigma - \alpha_i \phi}\right]$$

$$\text{Simplify}\left[\text{epeak}[[2, 1, 2]] > \frac{\delta \mu}{\mu \sigma - \alpha_i \phi}\right]$$

$$\sqrt{\alpha i} \delta \sqrt{\mu} \sqrt{\sigma} \sqrt{\phi} (-\mu \sigma + \alpha_i \phi) < 0$$

$$\sqrt{\alpha i} \delta \sqrt{\mu} \sqrt{\sigma} \sqrt{\phi} (-\mu \sigma + \alpha_i \phi) > 0$$

The term $(-\mu \sigma + \alpha_i \phi)$ is negative (because $\frac{\theta \sigma}{1 + \alpha i} - \delta - \frac{\alpha_i \theta \phi}{\mu + \alpha_i \mu} > 0 \implies \frac{\theta \sigma \mu}{1 + \alpha i} - \frac{\alpha_i \theta \phi}{1 + \alpha i} > 0 \implies \theta \sigma \mu - \alpha_i \theta \phi > 0 \implies \sigma \mu - \alpha_i \phi > 0$), so the second candidate peak e does not satisfy the necessary inequality.

We can show that the first candidate e leads to a peak, rather than a trough, by looking at the sign of the second derivative $n''(e)$ evaluated at the candidate e value. Because this second derivative is negative, this e corresponds to a peak.

`Simplify[D[nequil2[[1, 1, 2]], {e, 2}] /. {e -> epeak[[1, 1, 2]}]`

$$-\frac{2 \sigma^{3/2} \left(\sqrt{\mu} \sqrt{\sigma} - \sqrt{\alpha i} \sqrt{\phi} \right)^4}{\sqrt{\alpha i} \delta^3 \sqrt{\mu} \phi^{3/2}}$$

In other words, we have shown that there is an equilibrium value of energy e that maximizes pathogen load n . Since e is a strictly increasing function of θ , **that implies the existence of a unique value of θ that gives rise to this maximum equilibrium pathogen load.**