Solving the master equation of the transmission of macroparasites

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Macroparasites, vector-borne
Example: Life-cycle of *Onchocerca volvulus*

- Definite host
  - Adult parasite
    - Microfilariae
      - Larvae
        - ATP (Annual transmission potential)
          - L1
            - L2
              - Vector
                - ABR (Annual Biting Rate)
                  - L3
                    - L4
                      - Adult parasite
                        - Ms
                          - Mi
                            - Mh
Problems & Motivation
(The modellers' dilemma)

"... It is of course desirable to work with manageable models which maximize

generality, realism and precision

toward the overlapping but not identical goals of

understanding, predicting, and modifying nature.

But this cannot be done. ..."

--

Wishes, demands & constrictions

Deterministic model

*generality*

**understanding** Biology of disease

- Heterogeneities among parasites, vectors & hosts
- Discrete & finite distributions

**predicting** Intervention success

realism

Stochastic model

Parasite distributions often cannot be adequately characterized by the mean only:

Ingested $m_i$ per fly

<table>
<thead>
<tr>
<th>Ingested $m_i$ per fly</th>
<th>Relative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>200</td>
<td>0.2</td>
</tr>
<tr>
<td>300</td>
<td>0.3</td>
</tr>
<tr>
<td>400</td>
<td>0.4</td>
</tr>
<tr>
<td>500</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Model compartments & rates

\[ H_{w,v} \]

Number of hosts with \( v \) premature (developing L4) and \( w \) mature worms (adult worms).

\( v^+ \): maximum no. of premature worms in the host
\( w^+ \): maximum no. of mature worms in the host

\[ u^+ = 10, \ v^+ = 10, \ w^+ = 200, \ \sigma_w = 1/10 \text{ yr}, \ \sigma_H = 1/50 \text{ yr}, \ \mu_w = 1/\text{ yr} \]

\[ \mu_H \] will be calculated by the algorithm as the sum over all dying individuals, yielding a constant population size.
Acquisition, maturation & death of parasites

No. of adult worms \([0…w^+ = 200]\)

\[ \Lambda^u_{w,v} \]

No. of immature worms \([0…v^+ = 10]\)

\[ \mu_H \]

\[ \sigma_H \]

\[ \sigma_W \]

Note the assumption: hosts cannot harbour more than 10 L4 at the same time. This is a strong mechanism of limitation.
Transitions (only infection):

Host state before infection

- $H_{w,0}$
- $H_{w,1}$
- $H_{w,2}$
- $H_{w,3}$
- $H_{w,4}$
- $H_{w,5}$
- $H_{w,6}$

Host state after infection

No. of L3 transmitted:
- $u^+ = 3 \text{ L3}$
- $v^+ = 6 \text{ L4}$
- $w^+ = 3 \text{ adult worms}$

Example:
- $u = 1 \text{ L3}$
- $u = 2 \text{ L3}$
- $u = 3 \text{ L3}$

$H_{w,2}$ can originate from...
\[
\frac{dH_{w,2}}{dt} = \ldots + \sum_{i=0}^{1} H_{w,i} L_{w,i}^{2-i}
\]

In general:
\[
\frac{dH_{w,v}}{dt} = \ldots + \sum_{i=\text{Max}(0,v-u^+)}^{v-1} H_{w,i} L_{w,i}^{v-i}
\]

$H_{w,2}$ can become...
\[
\frac{dH_{w,2}}{dt} = \ldots - \sum_{u=1}^{3} H_{w,2} L_{w,2}^{u}
\]

In general:
\[
\frac{dH_{w,v}}{dt} = \ldots - \sum_{u=1}^{u^+} H_{w,v} L_{w,v}^{u}
\]

$H_{w,6}$ can originate from...
\[
\frac{dH_{w,6}}{dt} = \ldots + \sum_{v=6-3}^{6-1} \sum_{u=6-v}^{3} H_{w,6} L_{w,6}^{u}
\]

In general:
\[
\frac{dH_{w,v'}}{dt} = \ldots + \sum_{v=v'-u^+}^{v'-1} \sum_{u=1}^{u^+} H_{w,v'} L_{w,v'}^{u}
\]
Acquisition & death of parasites: model

\[
dH_{w,v} = \frac{dH_{w,v}}{dt} = -\sigma_H H_{w,v} - w\sigma_W H_{w,v} + (w+1)\sigma_W H_{w+1,v} - \sum_{u=1}^{u^+} H_{w,v} \Lambda^u_{w,v} + \sum_{i=\text{Max}(0,v-u^+)}^{v-1} H_{w,i} \Lambda^{v-i}_{w,i} - \nu \mu_v H_{w,v} + (v+1)\mu_v H_{w+1,v+1}
\]
Acquisition & death of parasites: equations

\[
\mu_H = \sum_{v=0}^{w^+} \sum_{w=0}^{v^+} \sigma_H(w) H_{v,w}
\]

Indices refer to compartments!

\[
\frac{dH_{0,0}}{dt} = \mu_H - \sigma_H(0) H_{0,0} + (0 + 1) \sigma_W H_{0+1,0} - \sum_{v=1}^{w^+} H_{0,v} \Lambda_{v,0}^W
\]

\[
\frac{dH_{0,v}}{dt} = -\sigma_H(0) H_{0,v} + (0 + 1) \sigma_W H_{0+1,v} - \sum_{w=1}^{v^+} H_{0,w} \Lambda_{v}^W + \sum_{i=\max(0,v-n^+)}^{\min(v^+,n^+)} H_{0+1,i} \Lambda_{v,i}^W - v_{\mu_Y} H_{0,v}
\]

\[
\frac{dH_{0,v^+}}{dt} = -\sigma_H(0) H_{0,v^+} + (0 + 1) \sigma_W H_{0+1,v^+} + \sum_{i=\max(0,v-n^+)}^{\min(v^+,n^+)} H_{0+1,i} \Lambda_{v,i}^W - v^+ \mu_Y H_{0,v^+}
\]
Acquisition & death of parasites: equations

\[ \frac{dH_{w,0}}{dt} = -\sigma_H(w)H_{w,0} - w\sigma_W H_{w,0} + (w + 1)\sigma_W H_{w+1,0} - \sum_{u=1}^{v-1} H_{w,u}\Lambda_{w,u}^\Sigma + (0 + 1)^{\mu_H} H_{w-1,0+1} \]

\[ \frac{dH_{w,v}}{dt} = -\sigma_H(w)H_{w,v} - w\sigma_W H_{w,v} + (w + 1)\sigma_W H_{w+1,v} - \sum_{u=1}^{v-1} H_{w,u}\Lambda_{w,u}^\Sigma + \sum_{i=\max(0,v-u)}^{v-1} H_{w+i}\Lambda_{w,i}^{v-i} - v^{\mu_H} H_{w,v} + (v + 1)^{\mu_H} H_{w-1,0+1} \]

\[ \frac{dH_{w,v+1}}{dt} = -\sigma_H(w)H_{w,v+1} - w\sigma_W H_{w,v+1} + (w + 1)\sigma_W H_{w+1,v+1} + \sum_{i=\max(0,v-u)}^{v-1} H_{w+i}\Lambda_{w,i}^{v-i} - v^{\mu_H} H_{w,v+1} \]
Acquisition & death of parasites: equations

\[
\begin{align*}
\frac{dH_{w^0,\nu}}{dt} &= -\sigma_H(w^0)H_{w^0,\nu} - w^+\sigma_W H_{w^0,\nu} \\
\frac{dH_{w^+,\nu}}{dt} &= -\sigma_H(w^+)H_{w^+,\nu} - w^+\sigma_W H_{w^+,\nu} \\
\frac{dH_{w^+,\nu}}{dt} &= -\sigma_H(w^+)H_{w^+,\nu} - w^+\sigma_W H_{w^+,\nu} + \sum_{\nu=1}^{v-1} H_{w^+,\nu} \Lambda_{w^+,\nu} - \nu H_{w^+,\nu} + (\nu + 1) \mu_H H_{w^+,\nu+1} \\
&+ \sum_{\nu=1}^{v-1} \sum_{i=v^0}^{v-1} H_{w^+,i} \Lambda_{w^+,i} - \nu^+ \mu_H H_{w^+,\nu} + (\nu + 1) \mu_H H_{w^+,\nu+1}
\end{align*}
\]
### Acquisition & death of parasites: equations

<table>
<thead>
<tr>
<th></th>
<th>Hosts are born</th>
<th>Hosts die</th>
<th>Parasites die</th>
<th>Parasites acquired</th>
<th>Parasites mature</th>
<th>Results</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-send +receive)</td>
<td>(-send +receive)</td>
<td>(-send +receive +receive borderline)</td>
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</tr>
<tr>
<td>( \frac{dH_{3,0}}{dt} )</td>
<td>( \mu_H ) - ( \sigma_{H}(0)H_{3,0} )</td>
<td>no send</td>
<td>( (0 + 1) \sigma_W H_{3+1,0} )</td>
<td>no receive</td>
<td>no send</td>
<td>no send</td>
<td>no receive borderline</td>
</tr>
<tr>
<td>( \frac{dH_{3,\gamma}}{dt} )</td>
<td>( -\sigma_{H}(0)H_{3,\gamma} )</td>
<td>no send</td>
<td>( (0 + 1) \sigma_W H_{3+1,\gamma} )</td>
<td>no receive</td>
<td>no receive</td>
<td>no receive borderline</td>
<td></td>
</tr>
<tr>
<td>( \frac{dH_{3,\gamma^+}}{dt} )</td>
<td>( -\sigma_{H}(0)H_{3,\gamma^+} )</td>
<td>no send</td>
<td>( (0 + 1) \sigma_W H_{3+1,\gamma^+} )</td>
<td>no receive</td>
<td>no receive</td>
<td>no receive borderline</td>
<td></td>
</tr>
<tr>
<td>( \frac{dH_{w,0}}{dt} )</td>
<td>( -\sigma_{H}(w)H_{w,0} ) - ( w \sigma_W H_{w,0} ) + ( (w + 1) \sigma_W H_{w+1,0} ) - ( \sum_{i=1}^{V-1} H_{w,0} L_{w,i}^0 )</td>
<td>no receive</td>
<td>no receive</td>
<td>no send</td>
<td>( (0 + 1) \mu_H H_{w-1,0+1} )</td>
<td>no receive borderline</td>
<td></td>
</tr>
<tr>
<td>( \frac{dH_{w,\gamma}}{dt} )</td>
<td>( -\sigma_{H}(w)H_{w,\gamma} ) - ( w \sigma_W H_{w,\gamma} ) + ( (w + 1) \sigma_W H_{w+1,\gamma} ) - ( \sum_{i=1}^{V-1} H_{w,\gamma} L_{w,i}^\gamma ) + ( \sum_{i=1}^{V-1} H_{w,i} L_{w,i}^{\gamma-1} ) - ( \gamma \mu_H H_{w,\gamma} ) ( + (v + 1) \mu_H H_{w-1,\gamma+1} )</td>
<td>no receive</td>
<td>no receive</td>
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<td>no receive borderline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \frac{dH_{w,\gamma^+}}{dt} )</td>
<td>( -\sigma_{H}(w)H_{w,\gamma^+} ) - ( w \sigma_W H_{w,\gamma^+} ) + ( (w + 1) \sigma_W H_{w+1,\gamma^+} )</td>
<td>no receive</td>
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<td>no receive borderline</td>
<td></td>
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</tr>
</tbody>
</table>

**Equations for a model of parasite acquisition and death:**

- **Hosts born:** Various factors affecting the birth of hosts and the acquisition of parasites.
- **Hosts die:** Model equations for the death of hosts.
- **Parasites die:** Equations for the death and maturation of parasites.
- **Parasites acquired:** Model equations for the acquisition of parasites by hosts.
- **Parasites mature:** Equations for the maturation of parasites.

The equations describe the dynamics of parasite acquisition and death in a host population, considering factors such as host birth, death, and parasite infection rates.
Frequency of people with $w$ adult worms

\[
H_w = \sum_{v=0}^{v^+} H_{v,w}
\]

No. of immature worms [0…$v^*$ =10]

No. of adult worms [0…$w^*$ =200]
Program

• Problems & Motivation
• Modeling approach
  – compartments
  – equations
  – distributions
• First results
• Outlook
Microfilaria production: $w \rightarrow m_s$

The microfilarial density $m_s$ is beta-binomial distributed with expectation $p_m \cdot m^+$ and a dispersion parameter $\beta$.

$$m_s(w) = p_m m^+$$

$w$ adult worms per person

$${p_m} = \frac{b w}{1 + b w}$$

$0 < b < 10$, $\beta = 2.0 \in [0.01...100.0]$, $m^+ = 500.0 \in [10.0...10000.0]$
MF ingested: $m_s \rightarrow m_i$

The log of microfilarial intake $m_i$ is betabinomial-distributed, with expectation $\mu$, Min, Max proportional to the log of $m_s$:

$\log(m_i + 1) = y_0 + s \log(m_s + 1)$

*Expectation:* $\mu = 10^{y_0} (m_s + 1)^{s} - 1$

*Minimum:* $m_{i,\text{min}} = \text{Max}[10^{y_0-s}(m_s + 1)^{s} - 1, 0]$

*Maximum:* $m_{i,\text{max}} = 10^{y_0+s}(m_s + 1)^{s} - 1$

$s = 0.62 \in [0.0...5.0], \ \beta = 22.2 \in [0.01...1000.0], \ y_0 = 0.38 \in [0.0...10.0]$
Flies die, dependent on $m_i$

A proportion of flies dies because of a natural mortality $d_0$, and an excess mortality caused by ingested MF. We assume that the ABR remains constant, i.e. these flies are replaced by "virgin" flies which have not yet taken a bloodmeal and are non-infected.

$$d(m_i) = d_0 + \left(1 - d_0\right) \frac{s m_i}{1 + s m_i}$$

$d_0 = 0.2, \in [0.0...1.0], \ s = 0.01, \in [0.0...0.1]$
Flies die, dependent on $m_i$

A proportion of flies dies because of a natural mortality $d_0$, and an excess mortality caused by ingested MF. We assume that the ABR remains constant, i.e. these flies are replaced by "virgin" flies which have not yet taken a bloodmeal and are non-infected.

$\mu = (10^{y_0} (m+1)^x - 1)(1-d)$
$p = \mu / m^+$

Distribution of $m_i$ conditional on $m_s$

Weighting with distribution of $m_s$

2-dimensional distribution

Marginal distribution

Distribution of $m_i$

Ingested $m_i$ per fly

Ingested $m_i$ per fly

Rel. frequency

Rel. frequency

Distribution of $m_i$ conditional on $m_s$

Prevalence of infected flies: 58%

$d_0 = 0.2, \in [0.0...1.0], \ s = 0.01, \in [0.0...0.1]$
Larval development: $m_i \rightarrow m_h$.

The no. of haemocoelic microfilariae $m_h$ per fly is a binomial sample of the no. of ingested $m_i$.

$\log_{10}(m_h + 1) = s \log_{10}(m_i + 1)$

$\rightarrow m_h = (m_i + 1)^s - 1$

Estimate: $s = 0.188$

Proportion developing: $p = m_h / m_i$

$s = 0.188, \in [0.0...10]$
Problems & Motivation
Modeling: compartments
Modeling: equations
Modeling: distributions
Results
Outlook

Result: distribution of $L_3$

Assumptions:
• all haemocoelic microfilariae $m_h$ will develop into $L_3$
• The unit "fly" is identical with the unit "bite": flies per person & year = bites per person & year (bppy)

E.g.: $ABR = 10000$

Haemocoelic $m_h / fly$
$L_3 / bite$

Scaling by the $ABR$
Assume: e.g. the population consists of

\[ H_{0,0} = 50\% \]
\[ H_{1,0} = 40\% \]
\[ H_{0,1} = 10\% \]

\[ \Lambda^{1} = 2000 \text{ bppy, with } u = 1 \text{ L3} \]

\[ \Lambda^{1}_{0,0} = 500 \text{ L3 / yr} \]

\[ \Lambda^{1}_{0,1} = 100 \text{ L3 / yr} \]

\[ \Lambda^{1}_{1,0} = 400 \text{ L3 / yr} \]

Thus, \( \Lambda^{u}_{v,w} = H^{u}_{v,w} \text{ bppy}(u) / 2 \)
Acquisition, maturation & death of parasites
Program

• Problems & Motivation
• Modeling approach
  – compartments
  – equations
  – distributions
• First results
• Outlook
software
Calibration

Problems & Motivation
Modeling: compartments
Modeling: equations
Modeling: distributions
Results
Outlook

ATP - ABR

MF prevalence - ATP

L3/fly - MF intensity

MF intensity - ATP

→ age classes?
Program

• Problems & Motivation

• Modeling approach
  – compartments
  – equations
  – distributions

• First results

• Outlook
What type of model is this?

<table>
<thead>
<tr>
<th>Property</th>
<th>Model type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same initial conditions $\rightarrow$ same output</td>
<td>Deterministic</td>
</tr>
<tr>
<td><em>Distributions</em> are modelled, not <em>means</em></td>
<td>Stochastic</td>
</tr>
<tr>
<td>The model is based on transition <em>rates</em>, not on transition <em>probabilities</em></td>
<td>Deterministic</td>
</tr>
<tr>
<td>The model assumes infinite population size</td>
<td>Rather deterministic</td>
</tr>
</tbody>
</table>

My suggestion: "Stochastically structured deterministic model"
Outlook

- Implement other features like immunosuppression
- Will age-groups compromise performance?
- Sensitivity analyses
- Stability analyses, investigation of breakpoints
- Eradicability
- Prototype simulator for parasitic diseases.