Chapter 9
Continuous-Time Age-Structured Models in Population Dynamics and Epidemiology

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Abstract We present continuous-time models for age-structured populations and disease transmission. We show how to use the method of characteristic lines to analyze the model dynamics and to write an age-structured population model as an integral equation model. We then extend to an age-structured SIR epidemic model. As an example we describe an age-structured model for AIDS, derive a formula for the reproductive number of infection, and show how important a role pair-formation plays in the modeling process. In particular, we outline the semi-group method used in an age-structured AIDS model with non-random mixing. We also discuss models for populations and disease spread with discrete age structure.

9.1 Why Age-Structured Models?

In the simplest models for a single population all members are assumed to be interchangeable. However, even the simplest models for disease transmission include structuring the population by disease state (susceptible, exposed, infective, or removed).

More advanced population models add some structure to the population such as specification of spatial location or age. Age is one of the most important characteristics in the modeling of populations and infectious diseases. Individuals with different ages may have different reproduction and survival capacities. Diseases may have different infection rates and mortality rates for different age groups [1].

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Individuals of different ages may also have different behaviours, and behavioural changes are crucial in control and prevention of many infectious diseases. Young individuals tend to be more active in interactions with or between populations, and in disease transmissions.

Sexually-transmitted diseases (STDs) are spread through partner interactions with pair-formations, and the pair-formations are clearly age-dependent in most cases. For example, most AIDS cases occur in the group of young adults.

Childhood diseases, such as measles, chicken pox, and rubella, are spread mainly by contacts between children of similar ages. More than half of the deaths attributed to malaria are in children under five years of age due to their weaker immune systems. This suggests that in models for disease transmission in an age structured population it is necessary to allow the contact rates between two members of the population to depend on the ages of both members.

In order to describe age-structured models for disease transmission we must first develop the theory of age-structured populations. In fact, the first models for age-structured populations [34] were designed for the study of disease transmission in such populations.

9.2 Modeling Populations with Age Structure

Let $\rho(t,a)$ be the age-density function at time t with $a \in [0, a_+]$, where $a_+ < \infty$ is the maximum age of individuals, or with $a \in [0, \infty)$ for convenience of mathematical description. Then $\int_{a_1}^{a_2} \rho(t,a)da$ is the number of individuals having ages in the interval $[a_1, a_2]$ at time t, and $\int_0^\infty \rho(t,a)da = P(t)$ is the total population size at t. Let β be the age specific fertility rate, or birth rate, so that $\int_{a_1}^{a_2} \beta\rho(t,a)da$ is the number of offspring produced by individuals with ages in $[a_1, a_2]$ in unit time at time t. Then $\int_0^\infty \beta\rho(t,a)da = B(t)$ is the total number of newborns, at time t. The age specific fertility may depend on the population density so that $\beta = \beta(a, \rho(t,a))$, or may depend on the total population so that $\beta = \beta(a, P)$. The reader should note that here β is not related to the contact rate for disease transmission in compartmental models introduced in earlier chapters. Here we assume the fertility to be time-independent. Let μ be the age specific mortality, or death rate, so that $\int_0^\infty \mu\rho(t,a)da$ is the total number of deaths at time t, occurring in one unit time. Similarly, the age specific mortality may depend on the population

density so that $\mu = \mu(a, \rho(t, a))$, or may depend on the total population size so that $\mu = \mu(a, P)$. Again we assume the mortality to be time-independent. In this chapter we consider the case in which both the fertility and mortality depend on the total population size rather than on the age-specific population density.

Suppose that the population changes from time t to $t + h$, with $h > 0$. The number of newborns in the time interval $[t, t + h]$ is $\int_t^{t+h} B(s)ds = \int_t^{t+h} \int_0^\infty \beta(\sigma, P)\rho(s, \sigma)d\sigma ds$. Note that the number of individuals who die at time $t + s$, having age less than or equal to $a + s$, is $\int_0^{a+s} \mu(\sigma, P)\rho(t + s, \sigma)d\sigma$. Then the total number of deaths in the time interval $[t, t + h]$ is $\int_0^h \int_0^{a+s} \mu(\sigma, P)\rho(t + s, \sigma)d\sigma ds$.

Let $N(t, a) = \int_0^a \rho(t, \sigma)d\sigma$ be the number of individuals having ages less than or equal to a at time t, and assume that there is no migration. Then the change in the population size from time t to $t + h$ is the total number of births minus the total number of deaths during the time interval $[t, t + h]$, that is,

$$N(t + h, a + h) - N(t, a) = \int_t^{t+h} B(s)ds - \int_0^h \int_0^{a+s} \mu(\sigma, P)\rho(t + s, \sigma)d\sigma ds. \tag{9.1}$$

The instantaneous rate of change of the population size is

$$\lim_{h\to 0} \frac{N(t + h, a + h) - N(t, a)}{h} = N_t(t, a) + N_a(t, a) = \int_0^a \rho_t(t, \sigma)d\sigma + \rho(t, a).$$

Dividing (9.1) by h and then letting $h \to 0$ yields

$$\int_0^a \rho_t(t, \sigma)d\sigma + \rho(t, a) = B(t) - \int_0^a \mu(\sigma, P)\rho(t, \sigma)d\sigma. \tag{9.2}$$

Setting $a = 0$ in (9.2), we have $\rho(t, 0) = B(t)$. Differentiating equation (9.2) with respect to a, we have

$$\rho_t(t, a) + \rho_a(t, a) = -\mu(a, P)\rho(t, a). \tag{9.3}$$

Then we arrive at the following system of a first order partial differential equation with corresponding initial and boundary conditions:

$$\begin{aligned} \rho_t(t, a) + \rho_a(t, a) &= -\mu(a, P)\rho(t, a), \\ \rho(t, 0) &= \textstyle\int_0^\infty \beta(a, P)\rho(t, a)da = B(t), \\ \rho(0, a) &= \phi(a), \end{aligned} \tag{9.4}$$

where $\phi(a)$ is the initial age distribution. For continuity at $(0, 0)$ it would be necessary to require that

$$\phi(0) = \int_0^\infty \beta(a, P)\phi(a)da,$$

but because it is possible to allow discontinuous solutions of (9.4) this requirement is usually ignored.

The partial differential equation in (9.4) is commonly called the Lotka–McKendrick equation [26, 42].

9.2.1 Solutions along Characteristic Lines

Fix t_0 and a_0 and consider the functions $\bar{\rho}(h) := \rho(t_0 + h, a_0 + h)$ and $\bar{\mu}(h) := \mu(a_0 + h, P(t_0 + h))$. This amounts to following the age cohort of members of the population with age a_0 at time t_0. Then equation (9.3) is equivalent to

$$\frac{d\bar{\rho}}{dh} + \bar{\mu}(h)\bar{\rho} = 0. \tag{9.5}$$

Solving (9.5) yields

$$\bar{\rho}(h) = \bar{\rho}(0)e^{-\int_0^h \bar{\mu}(\tau)d\tau}, \tag{9.6}$$

that is,

$$\rho(t_0 + h, a_0 + h) = \rho(t_0, a_0)e^{-\int_0^h \bar{\mu}(\tau)d\tau}. \tag{9.7}$$

For $a > t$, setting $(t_0, a_0) = (0, a - t)$ and $h = t$, we have

$$\rho(t, a) = \rho(0, a - t)e^{-\int_0^t \bar{\mu}(\tau)d\tau} = \phi(a - t)e^{-\int_0^t \mu(a-t+\tau, P(\tau))d\tau}, \tag{9.8}$$

and for $t > a$, setting $(t_0, a_0) = (t - a, 0)$ and $h = a$, we have

$$\rho(t, a) = \rho(t - a, 0)e^{-\int_0^a \bar{\mu}(\tau)d\tau} = B(t - a)e^{-\int_0^a \mu(\tau, P(t-a+\tau))d\tau}, \tag{9.9}$$

[17, 38, 42]. Then, we obtain the following expressions for solutions along the lines of characteristics for system (9.4):

$$\rho(t, a) = \begin{cases} \phi(a - t)e^{-\int_0^t \mu(a-t+\tau, P(\tau))d\tau}, & a > t, \\ B(t - a)e^{-\int_0^a \mu(\tau, P(t-a+\tau))d\tau}, & t > a. \end{cases} \tag{9.10}$$

Thus we have obtained an expression for the population density function for all (t, a) by following each age cohort along a characteristic line. Notice, however, that the solutions in (9.10) involve the total population size P which depends on $\rho(t, a)$.

9.2.2 Equilibria and the Characteristic Equation

One of the important properties in the study of population dynamics is the asymptotic behavior of the steady states or equilibria of the populations. For system (9.4), a steady state, or an equilibrium distribution, $\rho^*(a)$, satisfies the equations

$$\begin{aligned} \frac{d\rho^*(a)}{da} &= -\mu(a, P^*)\rho^*(a), \\ \rho^*(0) &= \int_0^\infty \beta(a, P^*)\rho^*(a)da, \\ P^* &= \int_0^\infty \rho^*(a)da. \end{aligned} \tag{9.11}$$

Suppose that system (9.11) has a solution $\rho^*(a)$. Then we can investigate the local stability of this steady state or equilibrium by linearization of system (9.4) about $\rho^*(a)$ as follows.

Let $y(t,a) = \rho(t,a) - \rho^*(a)$, and write $Y(t) = \int_0^\infty y(t,a)da$. Then substitution into (9.4) yields

$$y_t + y_a = \rho_t + \rho_a - \rho_a^* = -\mu(a, Y + P^*)\,(y + \rho^*) - \rho_a^*,$$

and

$$y(t,0) = \rho(t,0) - \rho^*(0) = \int_0^\infty \beta(a, Y + P^*)\,(y + \rho^*)\,da - \rho^*(0),$$

where $P^* = \int_0^\infty \rho^*(a)da$. For $\rho(t,a)$ near ρ^*, we have, using (9.11),

$$\begin{aligned} y_t + y_a &\approx -\mu(a, P^*)y - \mu(a, P^*)\rho^* - \rho^*\mu_P(a, P^*)Y - \rho_a^* \\ &= -\mu(a, P^*)y - \rho^*\mu_P(a, P^*)Y, \end{aligned} \tag{9.12}$$

and

$$\begin{aligned} y(t,0) &\approx \int_0^\infty (\beta(a, P^*)y + \rho^*(a)\beta_P(a, P^*)Y)\,da \\ &= \int_0^\infty \beta(a, P^*)y(t,a)da + \int_0^\infty \rho^*(a)\beta_P(a, P^*)daY(t) \\ &= \int_0^\infty K(a, \rho^*, P^*)y(t,a)da, \end{aligned} \tag{9.13}$$

where

$$K(a, \rho^*, P^*) = \beta(a, P^*) + \int_0^\infty \rho^*(\sigma)\beta_P(\sigma, P^*)d\sigma. \tag{9.14}$$

Hence, for $\rho(t,a)$ near ρ^*, we arrive at the linearized equation

$$y_t + y_a = -\mu(a, P^*)y - \rho^*\mu_P(a, P^*)\int_0^\infty y(t,a)da, \tag{9.15}$$

with the linearized integral boundary condition

$$y(t,0) = \int_0^\infty K(a, \rho^*, P^*)y(t,a)da. \tag{9.16}$$

Suppose further that $y(t,a) = u(a)e^{\xi(t-a)}$, and write $w = \int_0^\infty u(a)e^{-\xi a}da$. By substituting them into (9.15) and (9.16), respectively, we have

$$\begin{aligned}\frac{du(a)}{da} &= -\mu(a,P^*)u(a) - \rho^*\mu_P(a,P^*)e^{\xi a}\int_0^\infty u(a)e^{-\xi a}da \\ &= -\mu(a,P^*)u(a) - \rho^*\mu_P(a,P^*)e^{\xi a}w,\end{aligned} \tag{9.17}$$

and

$$u(0) = \int_0^\infty K(a,\rho^*,P^*)u(a)e^{-\xi a}da. \tag{9.18}$$

Solving (9.17), we have

$$u(a) = e^{-\int_0^a \mu(\alpha,P^*)d\alpha}\left(u(0) - E(\xi,a)\ w\right), \tag{9.19}$$

where

$$E(\xi,a) = \int_0^a e^{(\int_0^s \mu(\alpha,P^*)d\alpha + \xi s)}\rho^*\mu_P(s,P^*)ds.$$

Then substituting (9.19) into (9.18) and w, we obtain the following linear system

$$\begin{aligned}u(0) &= \textstyle\int_0^\infty Ke^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}da\ u(0) - \int_0^\infty Ke^{-\xi a}E(\xi,a)da\ w, \\ w &= \textstyle\int_0^\infty e^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}da\ u(0) - \int_0^\infty e^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}E(\xi,a)da\ w,\end{aligned}$$

or equivalently, the linear system

$$\begin{aligned}\left(1 - \textstyle\int_0^\infty Ke^{-(\int_0^a \mu(\alpha,P^*d\alpha+\xi a)}da\right)u(0) + \int_0^\infty Ke^{-\xi a}E(\xi,a)da\ w = 0, \\ \textstyle\int_0^\infty e^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}da\ u(0) - \left(1+\int_0^\infty e^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}E(\xi,a)da\right)w = 0,\end{aligned} \tag{9.20}$$

in the unknowns $u(0)$ and w. Hence, there exists a non-zero solution $(u(0),w)$ to system (9.20) if and only if

$$\begin{aligned}&\left(1 - \textstyle\int_0^\infty Ke^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}da\right)\left(1 + \int_0^\infty e^{-(\int_0^a \mu(\alpha,P^*)d\alpha+\xi a)}E(\xi,a)da\right) \\ &\quad + \textstyle\int_0^\infty Ke^{-\xi a}E(\xi,a)da\int_0^\infty e^{-(\mu+\xi)a}da = 0.\end{aligned} \tag{9.21}$$

Equation (9.21) is an equation in ξ. There exists a solution of the form $y(t,a) = u(a)e^{\xi(t-a)}$ of the linearization (9.15) and (9.16) if and only if there exists a solution ξ to equation (9.21). Equation (9.21) is called the characteristic equation of system (9.4) as in [9–11].

9.3 Age-Structured Integral Equations Models

Integral equations have also been used for modeling of age-structured populations. These integral equations can be derived from system (9.4), or more specifically from (9.10).

Write $\Pi(a,P) = e^{-\int_0^a \mu(\tau,P(t-a+\tau))d\tau}$. Then it follows from (9.10) that

$$\begin{aligned} B(t) = & \int_0^t \beta(a,P)\rho(t,a)da + \int_t^\infty \beta(a,P)\rho(t,a)da \\ = & \int_0^t \beta(a,P)\Pi(a,P)B(t-a)da + \int_t^\infty \beta(a,P)\frac{\Pi(a,P)}{\Pi(a-t,P)}\phi(a-t)da, \end{aligned} \tag{9.22}$$

and

$$\begin{aligned} P(t) = & \int_0^t \rho(t,a)da + \int_t^\infty \rho(t,a)da \\ = & \int_0^t \Pi(a,P)B(t-a)da + \int_t^\infty \frac{\Pi(a,P)}{\Pi(a-t,P)}\phi(a-t)da. \end{aligned} \tag{9.23}$$

The coupled equations (9.22) and (9.23) are a system of nonlinear integral equations. In general, it cannot be solved analytically. We consider two special cases as follows.

If the birth rate is age-independent and density-dependent, that is, if $\beta = \beta(P)$, then the equation for the total number of newborns becomes

$$B(t) = \int_0^\infty \beta(P(t))\rho(t,a)da = P(t)\beta(P(t)). \tag{9.24}$$

Substituting (9.24) into (9.23), we have

$$P(t) = \int_t^\infty \frac{\Pi(a,P(t))}{\Pi(a-t,P(t))}\phi(a-t)da + \int_0^t \Pi(a,P(t))P(t-a)\beta(P(t-a))da. \tag{9.25}$$

Equation (9.25) is a delayed integral equation.

If the death rate is age-independent and density-dependent, that is, if $\mu = \mu(P)$, then integration of the partial differential equation in (9.4) yields the nonlinear ordinary differential equation

$$P'(t) + P(t)\mu(P(t)) = B(t), \tag{9.26}$$

where $'$ denotes d/dt, which is coupled with the following integral equation for B derived from (9.22):

$$B(t) = \int_t^\infty \beta(a,P)\frac{\Pi(a,P)}{\Pi(a-t,P)}\phi(a-t)da + \int_0^t \beta(a,P)\Pi(a,P)B(t-a)da. \tag{9.27}$$

Under further assumptions, systems (9.24) and (9.25), or (9.26) and (9.27) may become analytically solvable. For example, if β and μ are both functions of total population size only, then $P(t)$ is obtained by solving the ordinary differential equation (9.26) with $B(t)$ given by (9.24).

Whereas system (9.22) and (9.23) cannot in general be solved analytically, the equilibrium age distributions provide useful information for the population dynamics.

At an equilibrium age distribution, $\rho^*(a)$, we write

$$P^* = \int_0^\infty \rho^*(a)da, \quad B^* = \int_0^\infty \beta(a, P^*)\rho^*(a)da, \tag{9.28}$$

which are constant. It follows from (9.11) that

$$\rho^*(a) = \rho^*(0)e^{-\int_0^a \mu(a,P^*)da} = B^*\Pi(a, P^*). \tag{9.29}$$

Substituting (9.29) into B^* in (9.28), we can solve for B^* to get

$$B^* = \int_0^\infty \beta(a, P^*)\rho^*(a)da = B^* \int_0^\infty \beta(a, P^*)\Pi(a, P^*)da. \tag{9.30}$$

Then there exists a positive solution B^* to equation (9.30) if and only if there exists positive P^* such that

$$\int_0^\infty \beta(a, P^*)\Pi(a, P^*)da = 1. \tag{9.31}$$

Define $R(P) = \int_0^\infty \beta(a, P)\Pi(a, P)da$, which is called the reproduction number and is an expected number of newborns that an individual produces over its lifetime when the total population size is P. At an equilibrium age distribution P^*, the reproduction number is equal to one.

Substituting (9.29) into P^* in (9.28), we have

$$P^* = B^* \int_0^\infty \Pi(a, P^*)da.$$

Notice that $\int_0^\infty \Pi(a, P^*)da$ is the average life expectancy of individuals, when the population is at the equilibrium P^*. Then the total population size P^* equals the total number of surviving newborns at the equilibrium.

9.3.1 The Renewal Equation

We consider a special case where the birth and death rates are density-independent such that $\beta = \beta(a)$ and $\mu = \mu(a)$. In this case

$$\Pi(a, P) = e^{-\int_0^a \mu(\sigma)d\sigma}$$

is a function of a only. Then equation (9.22) becomes the linear integral equation

$$B(t) = F(t) + \int_0^t L(t-a)B(a)da, \tag{9.32}$$

where

$$F(t) = \int_t^\infty \beta(a)\frac{\Pi(a)}{\Pi(a-t)}\phi(a-t)da, \quad L(t) = \beta(t)\Pi(t).$$

Equation (9.32) is a linear Volterra integral equation of the second kind. It is called the renewal equation or Lotka equation for the population [4, 26].

Because of the linearity of equation (9.32), we can use Laplace transformation techniques to investigate the properties of the dynamics of the population. Let $\widehat{B}(s)$, $\widehat{F}(s)$, and $\widehat{L}(s)$ be the Laplace transforms of $B(t)$, $F(t)$, and $L(t)$, respectively. Notice that the integral in (9.32) is the convolution of K and B. Then taking the Laplace transform of each term in (9.22), we have

$$\widehat{B}(s) = \widehat{F}(s) + \widehat{L}(s)\widehat{B}(s).$$

Solving for $\widehat{B}(s)$, we obtain

$$\widehat{B}(s) = \frac{\widehat{F}(s)}{1-\widehat{L}(s)} = \widehat{F}(s) + \frac{\widehat{F}(s)\widehat{L}(s)}{1-\widehat{L}(s)}. \tag{9.33}$$

Since $\widehat{F}(s)$ and $\widehat{L}(s)$ are analytic functions, the properties of $\widehat{B}(s)$ are determined by the property of $1-\widehat{L}(s)$.

It follows from

$$\widehat{L}(s) = \int_0^\infty \beta(a)\Pi(a)e^{-sa}da$$

that

$$\widehat{L}(0) = \int_0^\infty \beta(a)\Pi(a)da = R(0),$$

$$\frac{d\widehat{L}(s)}{ds} = -\int_0^\infty a\beta(a)\Pi(a)da < 0,$$

and

$$\lim_{s\to-\infty}\widehat{L}(s) = +\infty, \quad \lim_{s\to+\infty}\widehat{L}(s) = 0.$$

Hence there exists a unique $s_0 \in \mathbb{R}$ such that $\widehat{L}(s_0) = 1$. Whether s_0 is positive, zero, or negative, depends on whether $R(0)$ is greater than, equal to, or less than one.

Moreover, it is easy to check that if there exits a complex number $s = \alpha + i\gamma$ such that $\widehat{L}(s) = 1$, then it follows from the real part of $\widehat{L}(s) = 1$,

$$\int_0^\infty \beta(a)\Pi(a)e^{-\alpha a}\cos\gamma a da = 1 = \int_0^\infty \beta(a)\Pi(a)e^{-s_0 a}da,$$

that $\alpha \leq s_0$.

Hence s_0 is a dominant root of $\widehat{L}(s) = 1$. With this dominant root, s_0, it can be shown that

$$B(t) = b_0 e^{s_0 t}\left(1 + \Omega_1(t)\right), \quad P(t) = p_0 e^{s_0 t}\left(1 + \Omega_2(t)\right),$$

where $b_0 \geq 0$ and $p_0 \geq 0$ are real numbers, and $\lim\limits_{t\to\infty} \Omega_k(t) = 0$, $k = 1, 2$. (See, e.g., [26, Sect. I, 5].)

Therefore, the location of s_0 determines the asymptotic behavior of the population. Equation $\widehat{K}(s) = 1$ is called the Lotka characteristic equation for the renewal equation (9.32).

Now that we have an understanding of age-structured population models, we can begin to study age-structured disease transmission models.

9.4 Age-Structured Epidemic Models

Suppose that we have an age-structured population described by (9.4) in which there is an infectious disease of SIR type. We introduce functions $S(t, a), I(t, a), R(t, a)$ representing the age distribution at time t of susceptible, infective, and removed members, respectively, so that

$$S(t, a) + I(t, a) + R(t, a) = \rho(t, a).$$

As we have seen, the rate of change in time of a function $X(t, a)$ of time and age is

$$X_t(t, a) + X_a(t, a).$$

Thus we may write a system of equations

$$\begin{aligned} S_t(t, a) + S_a(t, a) &= -\left(\mu(a) + \lambda(t, a)\right) S(t, a), \\ I_t(t, a) + I_a(t, a) &= \lambda(t, a)S(t, a) - \left(\mu(a) + \gamma(a) + \delta(a)\right) I(t, a), \\ R_t(t, a) + R_a(t, a) &= -\mu(a)R(t, a) + \gamma(a)I(t, a), \end{aligned}$$

to describe the transmission dynamics of the disease in the age-structured population. Here $\mu(a)$ is the natural death rate in each class, $\gamma(a)$ is the recovery rate, $\delta(a)$ is the disease death rate, and $\lambda(t, a)$ represents the infection rate. To this system of partial differential equations we must add the initial conditions

$$S(0, a) = \Phi(a), \quad I(0, a) = \Psi(a), \quad R(0, a) = 0, \tag{9.34}$$

where Φ and Ψ are the initial distributions of susceptibles and infectives, respectively. In addition there is the birth or renewal condition (assuming that the age-dependent birth rate does not depend on disease status and that all newborns are in the susceptible class).

$$S(t,0) = \int_0^\infty \beta(a)\rho(t,a)da. \tag{9.35}$$

Further analysis requires some assumption on the nature of the infection term $\lambda(t,a)$. One possibility is *intracohort* mixing,

$$\lambda(t,a) = f(a)I(t,a),$$

corresponding to the assumption that infection can be transmitted only between individuals of the same age. Another possibility is *intercohort* mixing,

$$\lambda(t,a) = \int_0^\infty b(a,\alpha)I(t,\alpha)d\alpha,$$

with $b(a,\alpha)$ giving the rate of infection from contacts between an infective of age α with a susceptible of age a. For intercohort mixing it is necessary to make further assumptions on the mixing, that is, on the nature of the function $b(a,\alpha)$. One possibility here would be separable pair formation,

$$b(a,\alpha) = b_1(a)b_2(\alpha).$$

Rather than pursuing the general analysis further here, we refer the reader to more advanced references such as [26], and turn to an example that will illustrate the main ideas.

9.5 A Simple Age-Structured AIDS Model

Consider a simple age-structured epidemic model in which HIV/AIDS is spread in a homosexual population of ages in $[a_0, \infty]$, where a_0 is the minimal sexually active age. We divide the population into the groups of susceptible individuals, infective individuals, and AIDS cases, denoted by S, I, and A, respectively.

Assume that there is an input flow, $\Lambda(a)$ for all ages a, entering only the susceptible group. For this simple model, we further assume that the number of susceptible individuals of age a_0 is a constant B, and that no individuals with age a_0 are infected yet. Let $\mu(a)$ be the natural death rate of all individuals in the population, $\gamma(a)$ the HIV developing rate for infective individuals, and $\delta(a)$ the AIDS induced death rate of AIDS cases. Then the transmission dynamics of the disease are governed by the following system of

equations [24]:

$$S_t(t,a) + S_a(t,a) = \Lambda(a) - (\mu(a) + \lambda(t,a))\, S(t,a), \tag{9.36a}$$
$$S(t,a_0) = B, \tag{9.36b}$$
$$S(0,a) = \Phi(a), \tag{9.36c}$$

$$I_t(t,a) + I_a(t,a) = -(\mu(a) + \gamma(a))\, I(t,a) + \lambda(t,a)S(t,a), \tag{9.36d}$$
$$I(t,a_0) = 0, \tag{9.36e}$$
$$I(0,a) = \Psi(a), \tag{9.36f}$$

$$A_t(t,a) + A_a(t,a) = -\delta(a)A(t,a) + \gamma(a)I(t,a), \tag{9.36g}$$
$$A(t,a_0) = 0, \tag{9.36h}$$
$$A(0,a) = 0, \tag{9.36i}$$

where Φ and Ψ are the initial distributions of susceptibles and infectives, respectively.

The infection rate, λ, is determined by

$$\lambda(t,a) = r(a) \int_{a_0}^{\infty} \beta(a,a')\rho(t,a,a') \frac{I(t,a')}{T(t,a')} da', \tag{9.37}$$

where $T(t,a) = S(t,a) + I(t,a)$ is the total number of sexually active individuals, $r(a)$ the number of partners that an individual of age a has per unit time, $\beta(a,a')$ the transmission probability of a susceptible individual of age a infected by an infected partner of age a', and $\rho(a,a',t)$ the rate of pair-formation between individuals of ages a and a'.

The transmission probability can be further described by

$$\beta(a,a') = f(a)g(a'),$$

where $f(a)$ is the susceptibility of individuals of age a, and $g(a')$ is the infectiousness of individuals of age a'. Then

$$\lambda(t,a) = r(a)f(a) \int_{a_0}^{\infty} g(a')\rho(t,a,a') \frac{I(t,a')}{T(t,a')} da'. \tag{9.38}$$

9.5.1 The Reproduction Number

One of the fundamental questions of mathematical epidemiology is to find the reproduction number, which determines whether an infectious disease spreads in a susceptible population when the disease is introduced into the

population [1,13–15,19,21,23,37,41]. A possible formula for the reproduction number can be derived by determination of the condition for local stability of the infection-free equilibrium [4, 25, 28].

Model (9.36) has an infection-free equilibrium, $(S, I, A) = (S^0(a), 0, 0)$, where

$$S^0(a) = Be^{-M(a)} + e^{-M(a)} \int_{a_0}^{a} e^{M(x)} \Lambda(x) dx$$

with $M(a) = \int_{a_0}^{a} \mu(s) ds$.

We assume a separable pair-formation such that

$$\rho(t, a, a') = p_1(a) p_2(a').$$

Then we perturb the infection-free equilibrium by letting $u(t, a) = S(t, a) - S^0(a)$. Substitution into (9.37) leads to

$$\begin{aligned} \lambda(t, a) &= r(a) f(a) p_1(a) \textstyle\int_{a_0}^{\infty} g(a') p_2(a') \dfrac{I(t, a')}{T(t, a')} da' \\ &\approx r(a) f(a) p_1(a) \textstyle\int_{a_0}^{\infty} \dfrac{g(a') p_2(a')}{S^0(a')} I(t, a') da' := \tilde{\lambda}(t, a). \end{aligned}$$

Then linearizing system (9.36) yields the linear system:

$$\begin{aligned} u_t + u_a &= -\mu(a) u - \tilde{\lambda}(t, a) S^0(a), \\ I_t + I_a &= -\left(\mu(a) + \gamma(a)\right) I + \tilde{\lambda}(t, a) S^0(a), \\ A_t + A_a &= -\delta(a) A + \gamma(a) I. \end{aligned} \tag{9.39}$$

Assume

$$u(t, a) = \tilde{u}(a) e^{c(t-a)}, \quad I(t, a) = \tilde{I}(a) e^{c(t-a)}.$$

Then $\tilde{u}(a)$ and $\tilde{I}(a)$ satisfy the following system of ordinary differential equations:

$$\frac{d\tilde{u}(a)}{da} = -\mu(a) \tilde{u}(a) - b(a) e^{ca} W, \tag{9.40}$$

$$\frac{d\tilde{I}(a)}{da} = -\left(\mu(a) + \gamma(a)\right) \tilde{I}(a) + b(a) e^{ca} W, \tag{9.41}$$

where $b(a) = S^0(a) r(a) f(a) p_1(a)$, and

$$W = \int_{a_0}^{\infty} \frac{g(a') p_2(a')}{S^0(a')} e^{-ca'} \tilde{I}(a') da'. \tag{9.42}$$

Solving (9.41), we have

$$\tilde{I}(a) = W e^{-M(a) - \Gamma(a)} \int_{a_0}^{a} e^{M(s) + \Gamma(s)} b(s) e^{cs} ds, \tag{9.43}$$

with $\Gamma(a) = \int_{a_0}^{a} \gamma(v)dv$. Substituting (9.43) into (9.42), we obtain

$$W = W \int_{a_0}^{\infty} \frac{g(a')p_2(a')}{S^0(a')} e^{-M(a')-\Gamma(a')} \int_{a_0}^{a'} e^{M(s)+\Gamma(s)} b(s) e^{-c(a'-s)} ds da'. \tag{9.44}$$

Define

$$H(c) = \int_{a_0}^{\infty} \frac{g(a')p_2(a')}{S^0(a')} e^{-M(a')-\Gamma(a')} \int_{a_0}^{a'} e^{M(s)+\Gamma(s)} b(s) e^{-c(a'-s)} ds da'. \tag{9.45}$$

Then there exists a nonzero solution W to equation (9.44) if and only if there exists a real or complex number c such that

$$H(c) = 1. \tag{9.46}$$

For all real numbers c, we have $\lim_{c\to\infty} H(c) = 0$. Then it follows from

$$\begin{aligned} \tfrac{dH(c)}{dc} = & -\int_{a_0}^{\infty} \frac{g(a')p_2(a')}{S^0(a')} e^{-M(a')-\Gamma(a')} \\ & \cdot \int_{a_0}^{a'} (a'-s) e^{M(s)+\Gamma(s)} b(s) e^{-c(a'-s)} ds da' < 0, \end{aligned}$$

that $H(c)$ is a decreasing function. Hence, if c is a real solution of equation (9.46), then $c > 0$, provided $H(0) > 1$, and $c < 0$, provided $H(0) < 1$.

Suppose $c = \alpha + i\gamma$ is a complex solution of equation (9.46). Then substituting it into (9.46) and separating the real and imaginary parts yields

$$\begin{aligned} 1 = \mathrm{Re}H(c) = & \int_{a_0}^{\infty} \frac{g(a')p_2(a')}{S^0(a')} e^{-M(a')-\Gamma(a')} \\ & \cdot \int_{a_0}^{a'} e^{M(s)+\Gamma(s)} b(s) e^{-\alpha(a'-s)} \cos\gamma(a'-s) ds da' \le H(\alpha). \end{aligned}$$

If $H(0) < 1$, then $\alpha < 0$. Hence $H(0) = 1$ is a threshold for the stability of the infection-free equilibrium. Define $R_0 = H(0)$. Then R_0 is the reproduction number of infection for system (9.36). Equation (9.46) is called the characteristic equation.

9.5.2 Pair-Formation in Age-Structured Epidemic Models

Sexually transmitted diseases (STDs) spread through sexual activities between partners. The pair-formation, or mixing, is one of the key terms in modeling of STDs [18, 23]. In Sect. 9.5.1, we assume the function describing pair-formation in model (9.36) to be separable, which makes the mathematical

analysis more tractable. However, it has been shown that the assumption of a separable pair-formation function is equivalent to assuming a total proportionate or random partnership formation [2, 3, 5–7]. We briefly explain it as follows.

Let $\rho(t, a, a')$ be the pair-formation or mixing, which is the proportion of partners with age a' that an individual of age a has at time t. Let $r(t, a)$ be the average number of partners that an individual of age a has per unit of time, and let $T(t, a)$ be the total number of individuals of age a at time t. Then the function $\rho(t, a, a')$ has the properties

1. $0 \leq \rho(t, a, a') \leq 1$,
2. $\int_0^\infty \rho(t, a, a')da' = 1$,
3. $\rho(t, a, a')r(t, a)T(t, a) = \rho(t, a', a)r(t, a')T(t, a')$,
4. $r(t, a)T(t, a)r(t, a')T(t, a') = 0 \Longrightarrow \rho(t, a, a') = 0$.

Properties (1) and (2) follow from the fact that $\rho(t, a, a')$ is a proportion so that it is always between zero and one, and its total sum equals one. Property (3) comes from the fact that the total number of pairs of individuals of age a with individuals of age a' needs to be equal to the total number of pairs of individuals of age a' with individuals of age a. Moreover, if there are no active individuals, then there is no pair-formation, which leads to property (4).

9.5.2.1 Total Proportionate Mixing

Suppose that the pair-formation is a separable function such that

$$\rho(t, a, a') = \rho_1(t, a)\rho_2(t, a'). \tag{9.47}$$

It follows from property 2) that

$$\int_0^\infty \rho(t, a, a')da' = \int_0^\infty \rho_1(t, a)\rho_2(t, a')da' = \rho_1(t, a)\int_0^\infty \rho_2(t, a')da' = 1,$$

for all t. Hence

$$\rho_1(t, a) = \frac{1}{\int_0^\infty \rho_2(t, a')da'}$$

is independent of a. Denote it by $L(t)$. Then

$$\rho(t, a, a') = L(t)\rho_2(t, a'). \tag{9.48}$$

It follows from property 3) and (9.48) that

$$L(t)\rho_2(t, a')r(t, a)T(t, a) = \rho(t, a', a)r(t, a')T(t, a'). \tag{9.49}$$

Integrating (9.49) with respect to a from 0 to ∞ yields

$$L(t)\rho_2(t,a')\int_0^\infty r(t,a)T(t,a)da = r(t,a')T(t,a'). \tag{9.50}$$

Hence

$$L(t)\rho_2(t,a') = \frac{r(t,a')T(t,a')}{\int_0^\infty r(t,a)T(t,a)da}, \tag{9.51}$$

which implies that $\rho(t,a,a')$ satisfies

$$\rho(t,a,a') = \frac{r(t,a')T(t,a')}{\int_0^\infty r(t,a)T(t,a)da}. \tag{9.52}$$

Notice that the right-hand side in (9.52) is the fraction of the total partners of age a' in the population, or the availability of partners of age a'. A pair-formation or mixing function satisfying (9.49) is called a total proportionate mixing. Such a mixing depends completely on the availability of partners and is a kind of random mixing. While it may be appropriate to assume a proportionate mixing or random mixing in special cases such as modeling of HIV/AIDS for homosexual men, in general, it is necessary to assume the pair-formation or mixing function to be non-separable.

9.5.3 The Semigroup Method

As we have suggested in Sect. 9.5.2.1, in general the mixing function should be assumed non-separable. The mathematical analysis then becomes more difficult. A possible way to investigate dynamical behavior of models with non-separable mixing is to utilize the semigroup method. We outline the method for a simplified age-structured HIV/AIDS model with non-separable mixing as follows.

Consider ages in a finite interval $[0,\omega]$, where ω is the maximal sexually active age and assume the infection rate has the form

$$\lambda(t,a) = h(a)\int_0^\omega \rho(a,a')\frac{I(t,a')}{T(t,a')}da'.$$

Let $x = S/T$ and $y = I/T$. Then the dynamics of the age-structured epidemic model can be determined by the equation

$$y_t(t,a) + y_a(t,a) = (-\gamma(a)y + \lambda(t,a)) \tag{9.53}$$

with infection rate

$$\lambda(t,a) = h(a)\int_0^\omega \rho(a,a')y(t,a')da'. \tag{9.54}$$

Linearizing equation (9.53) with (9.54), we have

$$y_t + y_a = -\gamma(a)y + h(a)\int_0^\omega \rho(a,a')y(t,a')da'. \tag{9.55}$$

Define linear operators $\mathcal{B}$ and $\mathcal{P}$ by

$$\begin{aligned}(\mathcal{B}f)(a) &= -\frac{df(a)}{da} - \gamma(a)f(a),\\ (\mathcal{P}f)(a) &= h(a)\textstyle\int_0^\omega \rho(a,a')f(a')da'.\end{aligned}$$

Then equation (9.55) can be written as

$$\frac{dy}{dt} = (\mathcal{B}+\mathcal{P})\, y. \tag{9.56}$$

The operator $\mathcal{B}+\mathcal{P}$ generates a C_0 semigroup $T(t)$, for $t \geq 0$, and the semigroup $T(t)$ is eventually uniformly continuous. The growth bound of $T(t)$ is the spectral bound of $\mathcal{B}+\mathcal{P}$. It can be shown [27, 29, 33] that the resolvent of $\mathcal{B}+\mathcal{P}$, denoted by $R(\lambda;\mathcal{B}+\mathcal{P})$, is equal to $(S_\lambda - I)^{-1}G$ where

$$(Gf)(a) = \int_0^a e^{-\lambda(a-\sigma)}\Gamma(a)\Gamma^{-1}(\sigma)f(\sigma)d\sigma,$$

$$(S_\lambda f)(a) = \int_0^\omega \int_0^a e^{-\lambda(a-\sigma)}\Gamma(a)\Gamma^{-1}(\sigma)h(\sigma)p(\sigma,\xi)d\sigma f(\xi)d\xi.$$

Here we write $\Gamma(a) = e^{-\int_0^a \gamma(s)ds}$. Therefore, we can define the reproduction number of the epidemic, R_0, as the spectral radius of the operator

$$(Sf)(a) = \int_0^\omega \int_0^a \Gamma(a)\Gamma^{-1}(\sigma)h(\sigma)p(\sigma,\xi)d\sigma f(\xi)d\xi.$$

Consider a special case where the pair-formation is a finite sum of separable functions given by

$$\rho(a,a') = \sum_{j=1}^n p_j(a)q_j(a').$$

Then the reproduction number, R_0, is the largest positive eigenvalue λ_1 of the nonnegative matrix

$$\hat{K} = \begin{pmatrix} \int_0^\omega q_1(a)H_1(a)da & \cdots & \int_0^\omega q_1(a)H_n(a)da \\ & \vdots & \\ \int_0^\omega q_n(a)H_1(a)da & \cdots & \int_0^\omega q_n(a)H_n(a)da \end{pmatrix},$$

where

$$H_j(a) = \Gamma(a) \int_0^a h(\sigma)\Gamma^{-1}(\sigma)p_i(\sigma)d\sigma.$$

In particular, for $n = 2$, we have the explicit expression

$$\begin{aligned} R_0 = & \frac{1}{2}\int_0^\omega (q_1H_1 + q_2H_2)\, da \\ & + \frac{1}{2}\sqrt{\left(\int_0^\omega (q_1H_1 - q_2H_2)\, da\right)^2 + 4\int_0^\omega q_1H_2da \int_0^\omega q_2H_1da} \end{aligned}$$

for the reproduction number of infection [33].

9.6 Modeling with Discrete Age Groups

Under certain conditions, the age-structured partial differential equation model (9.4) can be reduced to a system of ordinary differential equations [22, 32, 40].

Partition the age interval into a finite number n of subintervals $[a_0, a_1)$, $[a_1, a_2), \cdots, [a_{n-1}, a_n)$, where $a_0 = 0$ and $a_n \leq \infty$. Denote the number of individuals with ages in interval $[a_{i-1}, a_i]$ by $H_i(t)$, so that $H_i(t) = \int_{a_{i-1}}^{a_i} \rho(t, a)da$, $i = 1, \cdots, n$. Then integrating the partial differential equation in (9.3) from a_0 to a_1, we have

$$\frac{dH_1(t)}{dt} + \rho(t, a_1) - \rho(t, a_0) + \int_{a_0}^{a_1} \mu(a, P)\rho(t, a)da = 0. \tag{9.57}$$

Assume that individuals with ages in each interval have the same vital rates such that $\beta(a, P) = \beta_i$, $\mu(a, P) = \mu_i$, for a in $[a_{i-1}, a_i]$, $i = 1, \cdots, n$. Here β_i and μ_i are age-independent, but may be density-dependent. Then, in the age interval $[0, a_1]$, we have

$$\rho(t, 0) = \sum_1^n \beta_i\ H_i(t), \quad \int_{a_0}^{a_1} \mu\ \rho(t, a)da = \mu_1\ H_1(t),$$

which leads to

$$\frac{dH_1}{dt} = \sum_1^n \beta_i\ H_i - (m_1 + \mu_1)H_1. \tag{9.58}$$

Here m_1 is the progression rate from groups 1 to 2, defined by $m_1 = \rho(t, a_1)/H_1(t)$, and we assume it is time-independent.

Integrating (9.3) from a_{i-1} to a_i for $2 \leq i \leq \infty$, we have

$$\frac{dH_i}{dt} = m_{i-1}\ H_{i-1} - (m_i + \mu_i)\, H_i, \quad i = 2, \cdots, n, \tag{9.59}$$

where m_i is the age progression rate from groups i to $i+1$, and we let $m_n = 0$. Then the system in (9.4) is reduced into a system of n ordinary differential equations.

9.6.1 Examples

We provide two simple examples to demonstrate how the discrete age group model described by equations (9.58) and (9.59) can be applied to populations and infectious diseases.

9.6.1.1 A Two-Age-Group Population Model

There are many means by which individuals of a species might compete for resources and by which intra-specific competition might express itself. Organisms which do not undergo such radical changes during their life cycles (e.g., birds, mammals, most reptiles, fishes, and hemimetabolous insects such as aphids, true bugs and grasshoppers) can experience considerable competition between juveniles and adults for common resources. Intra-specific competition can also occur to organisms with simple life cycles. The well studied flour beetles of genus *Tribolium* whose adult and larval stages utilize food resources in common provide a case in point [8].

Let $J(t)$ and $A(t)$ denote the densities of juveniles and adults at time t, respectively. Using the model in (9.58) and (9.59), with $n = 2$, we have the two age-group model

$$\begin{aligned} J'(t) &= \beta(J,A)A - (m(J,A) + \mu_1(J,A))\, J, \\ A'(t) &= m(J,A)J - \mu_2(J,A)A, \end{aligned} \tag{9.60}$$

where $'$ denotes d/dt, β is the birth rate of adults, μ_i, $i = 1, 2$, are death rates for juveniles and adults, respectively, and m is the age progression rate.

Models similar to (9.60) have been studied intensively. Readers are referred to [12, 16, 20, 30, 31, 35, 38, 39].

9.6.1.2 A Multi-Age-Group Malaria Model

Malaria is by far the world's most important tropical parasitic disease, which kills more people than any other communicable disease with the exception of tuberculosis. Approximately 10.5% (1,098,000) of deaths in children in developing countries in 2002 were due to malaria. Generally children have weaker immune systems, having not been as exposed to as much illness as adults.

It is known that there is acquired immunity in humans, even though the mechanisms of immunity to malaria are not fully understood. The acquired immunity appears to depend on both the duration and the intensity of past exposure to infection. Recovery from a primary infection with malaria does not imply fully protective immunity against reinfection. Immunity against malaria evidently influences the production of gametocytes. Frequency and intensity of gametocytemia decrease with increasing age until they reach a minimum among adults [43].

Therefore, in modeling of malaria transmission, age-structured models are more appropriate, and this can provide insight into the spread of malaria among different age groups, and can help identify efficient disease control strategies, for example, by targeting certain age-groups for vaccination.

Consider a human population in which malaria spreads. Divide the human population into four classes: susceptibles, exposeds who are the individuals infected but not yet transmitting the disease, infectives, and recovereds who are recovered and also immune from re-infection. Denote them as $S(a,t)$, $E(a,t)$, $I(a,t)$, and $R(a,t)$, respectively. We further divide the human population into n age groups such that S_i, E_i, I_i, and R_i, $i = 1,\dots,n$, are the susceptible, exposed, infective, and recovered individuals in age group i. Then the malaria transmission dynamics in the human population are governed by the system of ordinary differential equations

$$\begin{aligned}
S_1'(t) &= B(t) - (\mu_1+\eta_1)S_1 - \lambda_1(t)S_1,\\
S_j'(t) &= \eta_{j-1}S_{j-1} - \lambda_j(t)S_j - (\mu_j+\eta_j)S_j, \quad j = 2,\dots,n,\\
E_1'(t) &= \lambda_1(t)S_1 - (\mu_1+\epsilon_1+\eta_1)E_1,\\
E_j'(t) &= \lambda_j(t)S_j + \eta_{j-1}E_{j-1} - (\mu_j+\epsilon_j+\eta_j)E_j \quad j = 2,\dots,n,\\
I_1'(t) &= \epsilon_1 E_1 - (\mu_1+\gamma_1+\omega_1+\eta_1)I_1,\\
I_j'(t) &= \epsilon_j E_j + \eta_{j-1}I_{j-1} - (\mu_j+\gamma_j+\omega_j+\eta_j)I_j \quad j = 2,\dots,n,\\
R_1'(t) &= \gamma_1 I_1 - (\mu_1+\eta_1)R_1,\\
R_j'(t) &= \eta_{j-1}R_{j-1} + \gamma_j I_j - (\mu_j+\eta_j)R_j \quad j = 2,\dots,n,
\end{aligned} \tag{9.61}$$

where $B(t)$ is a input flow into the susceptible class, μ_i the age specific natural death rates, ω_i the age specific disease induced death rates, η_i the age progression rate, ε_i the age specific disease progression rates, and γ_i the age specific recovery rates.

The infection rates $\lambda_j(t)$ for humans are related to the vector (mosquito) population and are given by

$$\lambda_j(t) = \frac{bN_v(t)}{N(t)}\beta_j\frac{I_v(t)}{N_v(t)} = \frac{b\beta_j I_v(t)}{N(t)}, \quad j = 1,\dots,n, \tag{9.62}$$

where b is the number of bites on humans taken per mosquito in unit time, N_v the total mosquito population, $N = \sum_{j=1}^{n}(S_j+E_j+I_j+R_j)$ the total human

population, I_v the number of infective mosquitoes, and β_j the probability of infection for humans in group j.

Due to the short life span of the mosquito populations, age structure is not incorporated into the mosquitoes. It is also assumed that all mosquitoes will die before recovering from infection. Then $N_v = S_v + E_v + I_v$, where S_v and E_v are the numbers of susceptible and exposed mosquitoes. The dynamics of the mosquito population are described by the equations

$$\begin{aligned} S_v'(t) &= M_v - \lambda_v S_v - \mu_v S_v, \\ E_v'(t) &= \lambda_v(N_v - E_v - I_v) - (\mu_v + \varepsilon_v), \\ I_v'(t) &= \varepsilon_v E_v - \mu_v I_v, \end{aligned} \tag{9.63}$$

where M_v is an input flow of susceptible mosquitoes, μ_v is the natural death rate of mosquitoes, ε_v is the disease progression rate for exposed mosquitoes, and λ_v is the infection rate for mosquitoes given by

$$\lambda_v(t) = b \sum_{j=1}^{n} \left(\frac{\beta_{v_j} I_j(t)}{N(t)} \right). \tag{9.64}$$

Here β_{v_j} are the infection rate of mosquitoes by infected humans in group j.

System (9.61) is strongly coupled, which increases the difficulty of mathematical analysis. Readers are referred to [36] for preliminary studies.

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