# The genesis and use of time-varying frailty models for representing heterogeneities in the transmission of infectious diseases

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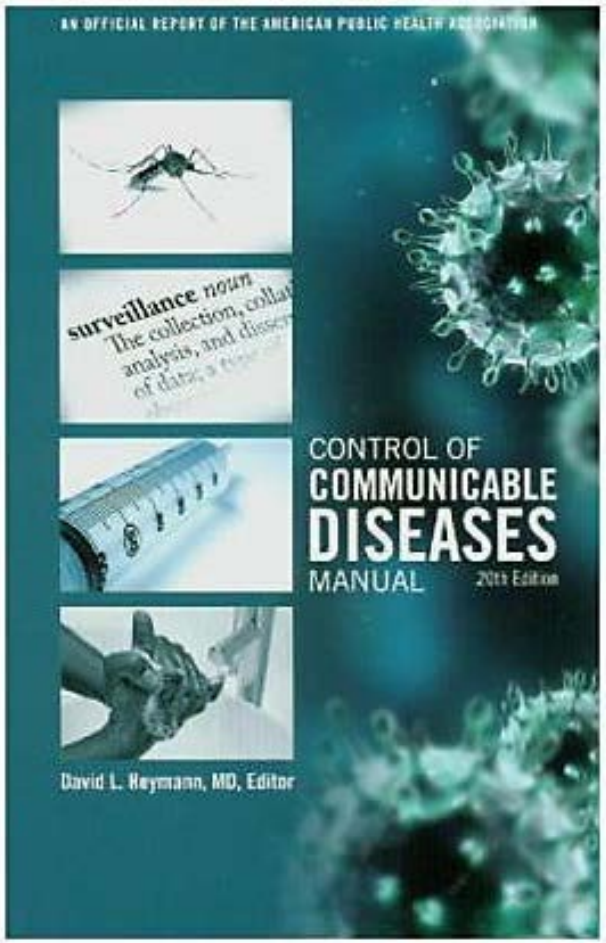
# Infectious diseases and their transmission




- Infectious diseases are caused by pathogenic biological agents.
- The spreading of infectious agents is called transmission.
- Example: measles is transmitted from person to person primarily by the airborne route.
- The majority of transmission models are deterministic compartmental models.

# The Susceptible-Infected-Recovered (SIR) model

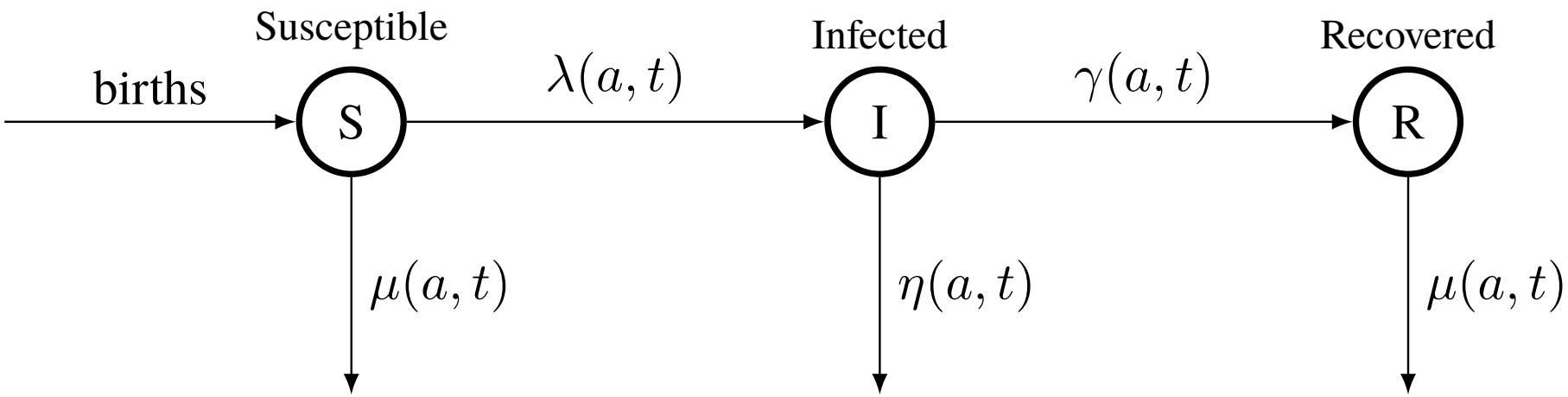



Figure: Flow diagram for the compartmental SIR model: Individuals are born into the susceptible class **S** and move to the infected state **I** at rate $\lambda(a,t)$, after which they recover and move to **R** at rate $\gamma(a,t)$. All individuals are subject to natural mortality at rate $\mu(a,t)$ and infected individuals to an additional disease-related mortality at rate $\alpha(a,t)$. It is assumed that $\eta(a,t) = \mu(a,t) + \alpha(a,t)$.

# Time-homogeneous SIR model

- The time-homogeneous SIR model can be described using the following set of ordinary differential equations (ODEs) in age:

$$\begin{aligned}
\frac{dS(a)}{da} &= -\left[\lambda(a) + \mu(a)\right] S(a) \ , \\
\frac{dI(a)}{da} &= \lambda(a)S(a) - \left[\gamma(a) + \eta(a)\right] I(a) \ , \\
\frac{dR(a)}{da} &= \gamma(a)I(a) - \mu(a)R(a) \ ,
\end{aligned}$$

  where $S(a)$, $I(a)$ and $R(a)$ represent the number of susceptible, infected and recovered individuals of age $a$.

- The total number of individuals of age $a$ in the population is $N(a) = S(a) + I(a) + R(a)$.

# Susceptible-Infected-Recovered-Susceptible (SIRS) model

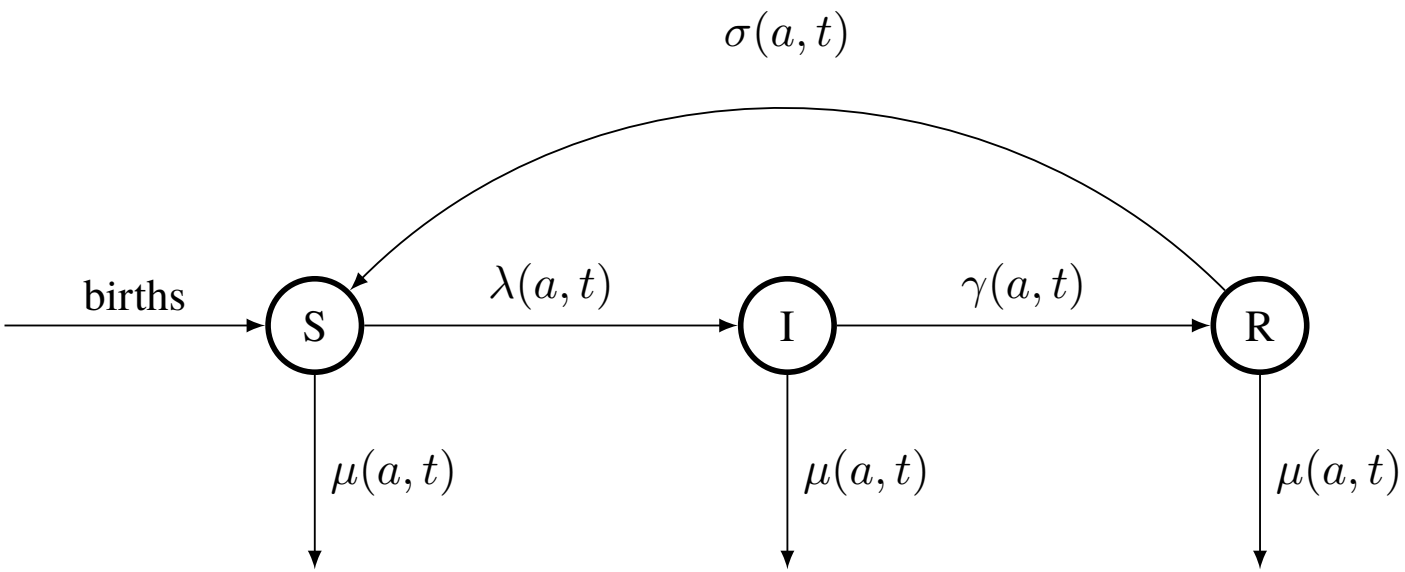



Figure: Flow diagram for the time-heterogeneous SIRS model: Individuals are born into the susceptible class **S** and move to the infected state **I** at rate $\lambda(a,t)$, after which they recover and move to **R** at rate $\gamma(a,t)$. Subsequently, individuals loose protective immunity and move back to **S** at replenishment rate $\sigma(a,t)$. All individuals are subject to natural mortality at rate $\mu(a,t)$.

# Heterogeneities in the transmission of infectious diseases

- Individuals in a population show variation with respect to properties that are relevant to the transmission of infections.
- Heterogeneities exist due to variation between individuals in
  - susceptibility to infection;
  - infectiousness, once infected;
  - activity levels in interacting with other individuals.
- Heterogeneity of a population may affect both
  1. the way in which infections are transmitted within it,
  2. and the effectiveness of strategies to control them.
- Allowing for individual heterogeneity in statistical and mathematical models of infectious diseases is important.

# How to quantify heterogeneities?

- Models often involve specifying contact rates between individuals.
- A contact is an event during which transmission of infection between two individuals could occur.
- For most types of infection, there is no event that can be clearly or uniquely defined as a contact.
- For these infections it is usually necessary to define a contact by some proxy variable.

# Quantifying heterogeneities: frailty modelling approach

- A different approach to make inferences on heterogeneities uses the fact that they leave an epidemiological footprint.
- The extent of heterogeneity in behaviour relevant to the transmission of infection will be reflected by the strength of the association between infections.
- The degree of heterogeneity can be estimated using multivariate frailty models for the hazard of infection.
- This approach enables us to observe the effects of heterogeneity without explicitly specifying the mechanisms that give rise to them.

# Modelling individual effects

- To facilitate the notation, it is assumed that age, denoted $a$, is the only measured attribute of an individual.
- Each individual has unobserved (latent) characteristics $\mathbf{z}$ with density $f(\mathbf{z})$; $\mathbf{z}$ comprises age-invariant random variables $z_1, \ldots, z_K$.
- We suppose that the age-dependent effect of the latent characteristics can be compounded into a single random variable $w(a, \mathbf{z})$, where $w(\cdot)$ is a deterministic function.
- For each $a$, $w(a, \mathbf{z})$ has mean 1. Of key importance in describing the degree of heterogeneity is the variance of $w(a, \mathbf{z})$.

# Effective contacts

- An effective contact is defined as an event involving individuals $X$ and $Y$ such that, if $Y$ was infectious and $X$ susceptible, then $Y$ would infect $X$.
- Let $\beta(a, \mathbf{z}; a', \mathbf{z}')$ represent the per-capita rate at which an individual with characteristics $(a', \mathbf{z}')$ makes effective contacts with individuals with characteristics $(a, \mathbf{z})$.
- The function $\beta(a, \mathbf{z}; a', \mathbf{z}')$ is non-negative and determines the so-called effective contact rate surface.

# Effective contact rate surface

- The effective contact rate surface may be written as

$$\beta(a, \mathbf{z}; a', \mathbf{z}') = \alpha(a, \mathbf{z}; a', \mathbf{z}')\beta_0(a, a') \ ,$$

where

$$\beta_0(a, a') = \int_{\mathbf{z}'} \int_{\mathbf{z}} \beta(a, \mathbf{z}; a', \mathbf{z}') f(\mathbf{z}) f(\mathbf{z}') \, \mathrm{d}\mathbf{z} \, \mathrm{d}\mathbf{z}'$$

is the average effective contact rate.

- We assume that $\alpha(a, \mathbf{z}; a', \mathbf{z}') = w(a, \mathbf{z})w'(a', \mathbf{z}')$, hence

$$\beta(a, \mathbf{z}; a', \mathbf{z}') = w(a, \mathbf{z})\beta_0(a, a')w'(a', \mathbf{z}') \ .$$

# Genesis of time-varying frailty models

- Let $\lambda(a, \mathbf{z}, t)$ be the hazard (or force) of infection acting on a susceptible individual of characteristics $(a, \mathbf{z})$ at time $t$.

- When the infection is in endemic equilibrium, the hazard of infection is of the form

$$\lambda(a, \mathbf{z}) = \int_0^\infty \int_{\mathbf{z}'} \beta(a, \mathbf{z}; a', \mathbf{z}') I(a', \mathbf{z}') \, \mathrm{d}\mathbf{z}' \, \mathrm{d}a' \quad ,$$

  where $I(a', \mathbf{z}')$ is the number of infectious individuals with characteristics $(a', \mathbf{z}')$.

- The functional form which is taken by $I(a', \mathbf{z}')$ depends on whether the infection is SIR, SIRS, or some other type.

# Genesis of time-varying frailty models

- The integral equation can be written as

$$\begin{aligned}\lambda(a,\mathbf{z}) &= \int_0^\infty \int_{\mathbf{z}'} w(a,\mathbf{z})\beta_0(a,a')w'(a',\mathbf{z}')I(a',\mathbf{z}')\,\mathrm{d}\mathbf{z}'\,\mathrm{d}a' \\ &= w(a,\mathbf{z}) \underbrace{\int_0^\infty \int_{\mathbf{z}'} \beta_0(a,a')w'(a',\mathbf{z}')I(a',\mathbf{z}')\,\mathrm{d}\mathbf{z}'\,\mathrm{d}a'}_{=\lambda_0(a)} \\ &= w(a,\mathbf{z}) \times \lambda_0(a) \ ,\end{aligned}$$

  where $\lambda_0(a)$ is the baseline force of infection.

- The equation above defines an age-varying frailty model for the hazard of infection with age-dependent frailty $w(a,\mathbf{z})$.

# Time-varying frailty models

## Bivariate setting:

- Consider two infections. For infection $j$ the force of infection at age $a$ for an individual with age-varying frailty $z_j(a)$ is assumed to be of the form

$$\lambda_j(a, z_j(a)) = z_j(a)\lambda_{0j}(a) \quad \text{for } j = 1, 2 \ ,$$

  where $\lambda_{0j}(a)$ are the baseline hazards.

- We still need to...
  1. find a function $w(a, z_{j1}, z_{j2}, \ldots, z_{jK}) = z_j(a)$, where $z_{jk}$ $(j = 1, 2; k = 1, \ldots, K)$ are independent age-invariant frailties;
  2. make a decision whether to use shared frailties with $z(a) := z_1(a) = z_2(a)$ or correlated frailties.

# Piecewise-constant frailties

- One could build piecewise-constant frailty models on disjoint age intervals $I_k = (a_{k-1}, a_k]$ for $k = 1, \ldots, K$ with $a_0 = 0$ and $a_K < \infty$.

- Let

$$z_j(a) = \sum_{k=1}^{K} z_{jk} I_k(a) \ ,$$

where $z_{jk} > 0$ are identically distributed with unit mean and variance $\gamma_{jk}$ $(j = 1, 2; k = 1, \ldots, K)$, and $I_k(a) = 1$ if $a \in I_k$ (with $I_k(a) = 0$ otherwise).

- Assumption: the frailty in age group $k$ is independent from the frailty in age group $k + 1$.

# Multiplicative family

- Consider the multiplicative family of models:

$$z_j(a) = \prod_{k=1}^{K} \left[1 + (z_{jk} - 1)\, h_{jk}(a)\right] \quad , \quad 0 \leq h_{jk}(a) \leq 1 \quad ,$$

where $z_{jk}$ for $j = 1, 2$ and $k = 1, \ldots, K$ are independent random variables with unit mean and variance $\gamma_{jk}$.

- The $h_{jk}(a)$ are deterministic functions such as

$$h_{jk}(a) = \exp\left[-(a\phi_{jk})^2\right] \quad ,$$

where $\phi_{jk} > 0$ is an exponential decay parameter.

- Assumption: the frailties across age groups are perfectly correlated.

# One-component time-varying shared frailty model

- Suppose that $K = 1$ and that the frailty components $z_{j1}$ $(j = 1, 2)$ follow a gamma distribution, denoted $\Gamma(\cdot, \cdot)$.

- In the shared frailty model, the correlation between the frailty terms $z_{11}$ and $z_{21}$ is unity we define $z_1 := z_{11} = z_{21}$.

- A one-component age-varying shared gamma frailty model is then

$$z(a) = [1 + (z_1 - 1)h_1(a)] \ ,$$

where $z_1 \sim \Gamma(\gamma_1^{-1}, \gamma_1^{-1})$.

# One-component time-varying correlated frailty model

- The correlated frailty model allows for a more flexible correlation structure among the frailty terms.

- One can build a one-component age-varying correlated gamma frailty model as follows:

$$z_j(a) = [1 + (z_{j1} - 1)h_{j1}(a)] \ ,$$

where $z_{j1} = \gamma_{j1}(y_{01} + y_{j1})$, $y_{l1} \sim \Gamma(k_{l1}, 1)$ and $\gamma_{j1} = (k_{01} + k_{j1})^{-1}$ $(j = 1, 2; l = 0, 1, 2)$.

- The implied correlation between between the frailty terms $z_{11}$ and $z_{21}$ is

$$\rho = \frac{k_{01}}{\sqrt{(k_{01} + k_{11})(k_{01} + k_{21})}} \ , \quad 0 \leq \rho \leq \min\left\{\sqrt{\frac{\gamma_{11}}{\gamma_{21}}}, \sqrt{\frac{\gamma_{21}}{\gamma_{11}}}\right\} \ .$$

# Bivariate serological survey data

- $T_1$ and $T_2$: ages at the onset of infection by two distinct infectious agents.
- Association between $T_1$ and $T_2$ can be examined using paired serological survey data on two infections.
- Data are obtained by testing blood serum residues for the presence of antibodies to one or more infections.
- A positive (negative) results indicates prior infection (lack of prior infection), giving rise to current status data.

# Observable data

- For current status data, only the information about whether the survival time of interest lies before or after the monitoring time (age) $a$ is available.

- Observed information in a bivariate setting is $\{a, \delta_1, \delta_2\}$, where

$$\delta_j = \begin{cases} 1 & \text{if} \quad T_j \leq a \\ 0 & \text{if} \quad T_j > a \end{cases}, \qquad (j = 1, 2) \quad .$$

- Aggregated data at each age $a$: $(n_{00a}, n_{01a}, n_{10a}, n_{11a})$ and $n_a = \sum_{i,j=0,1} n_{ija}$.

# Estimation

- Given parameterizations of $w(a, \mathbf{z})$, $\lambda_{01}(a)$ and $\lambda_{02}(a)$, the model is fitted by maximizing a multinomial likelihood.

- The multinomial log-likelihood kernel is

$$\sum_a \sum_{i,j=0,1} n_{ija} \ln \{p_{ij}(a)\} \quad ,$$

where the probabilities $p_{ij}(a)$ (in an SIR setting) are computed as

$$\begin{aligned}
p_{00}(a) &= \mathrm{E}\left(\exp\left\{-\int_0^a w(y,\mathbf{z})\left[\lambda_{01}(y)+\lambda_{02}(y)\right]\mathrm{d}y\right\}\right) \quad , \\
p_{01}(a) &= \mathrm{E}\left(\exp\left\{-\int_0^a w(y,\mathbf{z})\lambda_{01}(y)\,\mathrm{d}y\right\}\right) - p_{00}(a) \quad , \\
p_{10}(a) &= \mathrm{E}\left(\exp\left\{-\int_0^a w(y,\mathbf{z})\lambda_{02}(y)\,\mathrm{d}y\right\}\right) - p_{00}(a) \quad , \\
p_{11}(a) &= 1 - p_{01}(a) - p_{10}(a) - p_{00}(a) \quad .
\end{aligned}$$

# Fitting procedure for a pre-specified model

- For the current set of parameters,
  1. obtain the baseline hazards $\lambda_{0j}$ $(j = 1, 2)$,
  2. compute the probabilities $p_{00}(a)$, $p_{01}(a)$, $p_{10}(a)$ and $p_{11}(a)$,
  3. evaluate the log-likelihood,

  and iterate until convergence.

- Possible parameterizations of the baseline hazards include continuous parametric baselines (such as the Gompertz hazard) or piecewise constant baselines.

- For some of the models, the expressions $p_{ij}(a)$ for $i, j = 0, 1$ cannot be computed in closed-form.

# Applications

## Description of the data

1. Hepatitis A virus (HAV) and hepatitis B virus (HBV) serology
   - Different transmission routes.
   - Data obtained from a seroepidemiological study undertaken in 1993 and 1994 in Flanders, Belgium. In total, 4026 blood samples were drawn.
2. Parvovirus B19 and varizella zoster virus (VZV) serology
   - Similar transmission routes.
   - Data for 3379 individuals between 2001 and 2003 in Belgium.
   - Parvovirus B19: immunizing process (SIR) or recurrent infection process (SIRS).
   - Estimation of the basic reproduction number, $R_0$, from serological data and social contact data.
   - Social contact hypothesis: $\beta_0(a, a') = q \times c(a, a')$, where $q$ is an infection-specific proportionality factor.

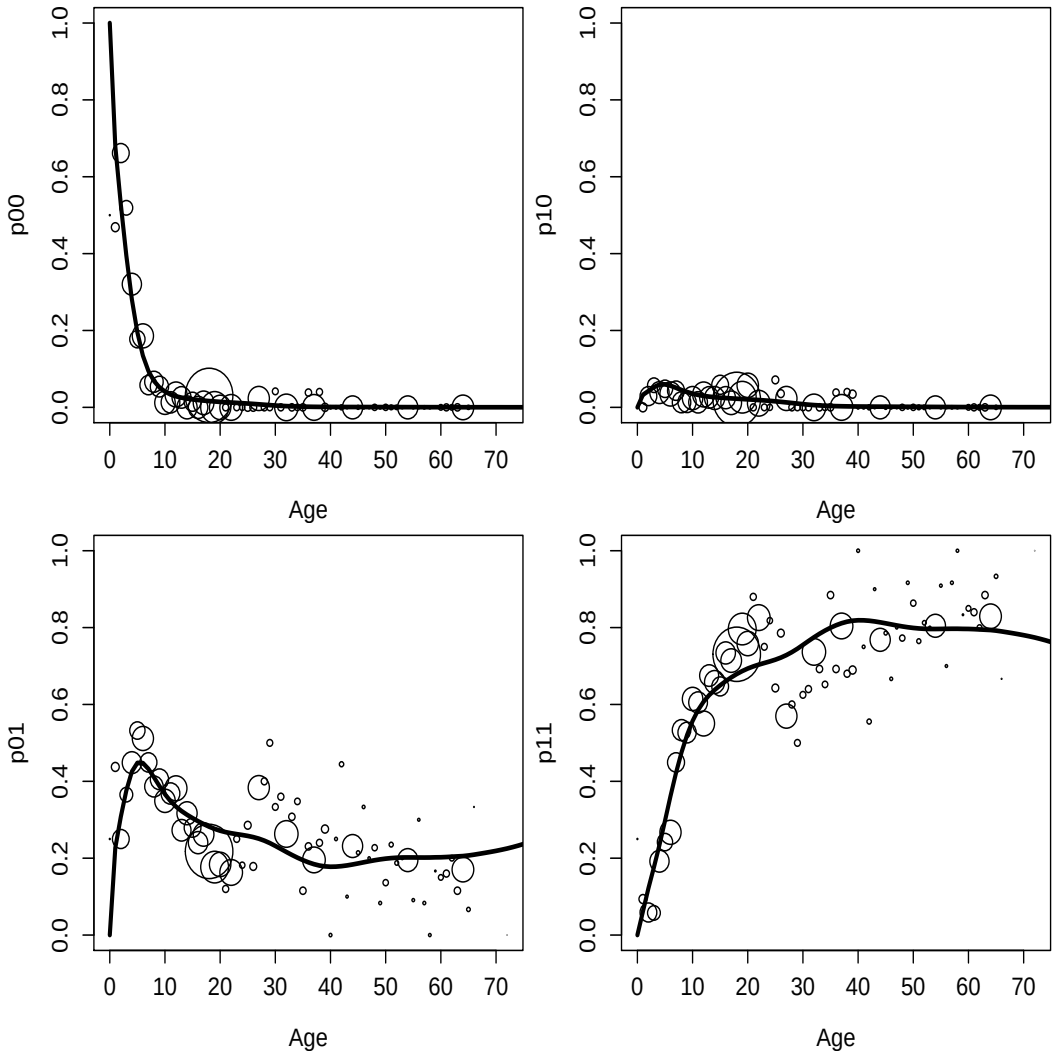
# Fitting results for HAV and HBV infection data

| Frailty model | Frailty parameters | Estimates (s.e.) | AIC | BIC |
|---|---|---|---|---|
| SGF | $\sqrt{\gamma_1}$ | 0.725 (0.086) | 5824.90 | 5856.41 |
| CGF | $\sqrt{\gamma_{11}}$ | 1.651 (0.176) | 5794.89 | 5828.99 |
| | $\sqrt{\gamma_{21}}$ | 1.608 (2.272) | | |
| | $\rho$ | 0.497 (0.702) | | |
| ADSGF-1C | $\sqrt{\gamma_1}$ | 5.843 (0.829) | 5756.01 | 5793.82 |
| | $\phi$ | 0.034 (0.005) | | |
| ADCGF-1C | $\sqrt{\gamma_{11}}$ | 6.606 (1.020) | 5757.04 | 5807.44 |
| | $\sqrt{\gamma_{21}}$ | 5.765 (0.831) | | |
| | $\phi$ | 0.025 (0.007) | | |
| | $\rho$ | 0.871 (0.080) | | |
| ADSGF-2C | $\sqrt{\gamma_1}$ | 5.814 (0.446) | 5758.03 | 5802.13 |
| | $\sqrt{\gamma_2}$ | 0.009 (0.124) | | |
| | $\phi$ | 0.034 (0.005) | | |
| ADPiecewiseSGF | $\sqrt{\gamma_1}$ | 3.671 (0.606) | 5749.01 | 5799.42 |
| | $\sqrt{\gamma_2}$ | 2.421 (0.504) | | |
| | $\sqrt{\gamma_3}$ | 0.012 (0.160) | | |
| | $\sqrt{\gamma_4}$ | 8.813 (7.856) | | |

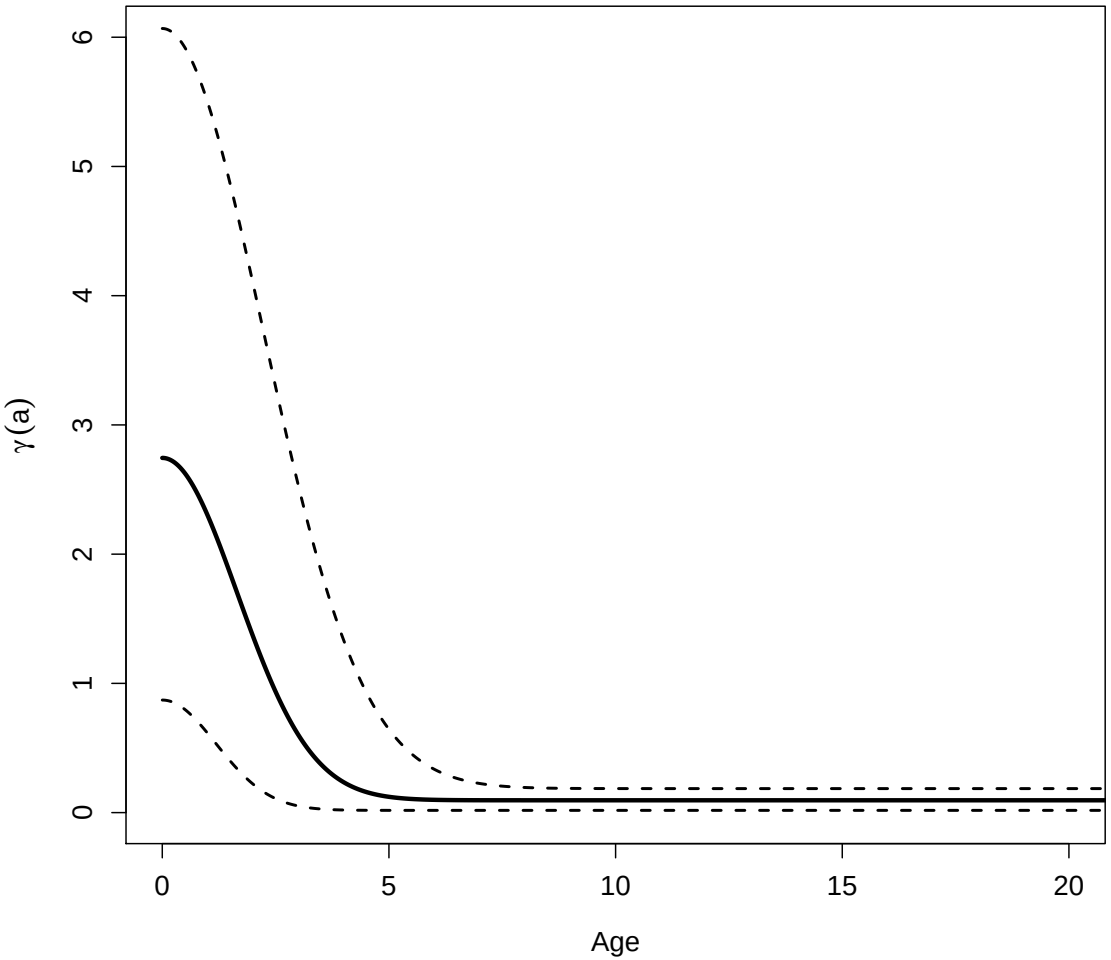
# Fitting results for Parvovirus B19 and VZV infection data

| Frailty model | Parameters | Estimates [CI] | $\hat{R}_0$ [CI] | AIC | BIC |
|---|---|---|---|---|---|
| SGF-SIR | $q_1$ | 0.072 [0.069, 0.075] | 3.60 [3.35, 3.88] | 4937.14 | 4955.51 |
| | $q_2$ | 0.200 [0.188, 0.214] | 11.64 [10.59, 12.82] | | |
| | $\gamma$ | 0.152 [0.118, 0.188] | | | |
| ADSGF-1C-SIR | $q_1$ | 0.072 [0.069, 0.076] | 3.60 [3.22, 3.99] | 4939.14 | 4963.64 |
| | $q_2$ | 0.200 [0.183, 0.221] | 11.64 [9.99, 13.49] | | |
| | $\gamma$ | 0.152 [0.100, 0.210] | | | |
| | $\phi$ | 0.000 [0.000, 0.009] | | | |
| ADSGF-2C-SIR | $q_1$ | 0.066 [0.062, 0.071] | 3.74 [3.15, 4.87] | 4912.08 | 4942.70 |
| | $q_2$ | 0.235 [0.191, 0.299] | 15.65 [11.38, 24.08] | | |
| | $\gamma_1$ | 2.918 [1.524, 5.004] | | | |
| | $\gamma_2$ | 0.233 [0.156, 0.323] | | | |
| | $\phi$ | 0.316 [0.246, 0.425] | | | |
| SGF-SIRS | $q_1$ | 0.071 [0.068, 0.074] | 3.18 [2.97, 3.43] | 4869.83 | 4894.33 |
| | $\sigma$ | 0.011 [0.008, 0.015] | | | |
| | $q_2$ | 0.173 [0.163, 0.183] | 8.98 [8.22, 9.83] | | |
| | $\gamma$ | 0.032 [0.002, 0.065] | | | |
| ADSGF-1C-SIRS | $q_1$ | 0.065 [0.061, 0.070] | 2.90 [2.64, 3.49] | 4862.93 | 4893.56 |
| | $\sigma$ | 0.012 [0.009, 0.016] | | | |
| | $q_2$ | 0.158 [0.141, 0.179] | 8.19 [7.15, 10.46] | | |
| | $\gamma$ | 1.470 [0.415, 3.498] | | | |
| | $\phi$ | 0.330 [0.209, 0.530] | | | |
| ADSGF-2C-SIRS | $q_1$ | 0.066 [0.062, 0.071] | 3.30 [2.79, 4.45] | 4859.26 | 4896.01 |
| | $\sigma$ | 0.011 [0.007, 0.015] | | | |
| | $q_2$ | 0.193 [0.156, 0.257] | 11.27 [8.11, 18.90] | | |
| | $\gamma_1$ | 2.419 [0.839, 4.960] | | | |
| | $\gamma_2$ | 0.095 [0.017, 0.186] | | | |
| | $\phi$ | 0.303 [0.226, 0.423] | | | |

# Observed and fitted seroprevalence of B19 and VZV



# Age-varying shared frailty variance



## Concluding remarks

- Time-varying frailty models are a natural choice for capturing individual heterogeneities relevant to the transmission of infectious diseases.
- Multivariate frailty models with shared/correlated frailties can be used for
  - inducing association between infection times within individuals,
  - heterogeneity among individuals.
- Central to our approach is the use of paired serological survey data on different infections for the same individuals.
- For pairs of infection with the same transmission route, a shared frailty model seems appropriate.
- Frailty modelling is fraught with lack of identifiability.
- Further work, some of it under way, is required in several areas.

# Research grant

- 3-year grant entitled "Frailty modelling for multivariate current status data with applications in epidemiology"
- Research project funded by the


- Aims:
  1. to develop innovative statistical approaches to analyse multivariate current status data,
  2. to develop estimation methods for the new models,
  3. to provide statistical software and examples of applications for the new methodologies.
- External collaborator: Niel Hens
- I am currently seeking a promising PhD student (or Postdoc) to work on this project.

# References

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