merlin: A framework and implementation(s) for extended mixed effects regression of linear, non-linear and user-defined models

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Outline

- My background
- Motivation for this work
- Extended multivariate generalised linear and non-linear mixed effects models
- `merlin`
- Methods development using `merlin`
- Future directions

My background

- MMath in Maths and Stats at University of St. Andrews, graduating in May 2009
- Awarded PhD in November 2014, titled "Development and application of methodology for the parametric analysis of complex survival and joint longitudinal-survival data in biomedical research"
- One year post-doc at Karolinska Institutet in Stockholm
- Appointed a Lecturer in March 2016 at Leicester
- Became Associate Professor in August 2018
- Now 20% seconded to Karolinska Institutet from this month

My background

- I mainly work in methodology; developing new statistical models and software
- My applied work is generally in cardiovascular disease and cancer
- My main areas of research are:
  - joint modelling of longitudinal and survival data
  - multi-state survival analysis
  - software development
- Development of methods for complex survival analysis, MRC NIRG Methodology Research Panel, March 2017 - March 2020

Motivation

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  - need for appropriate statistical modelling techniques, and implementations

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- The standard challenges
  - time-dependent effects, non-linear covariate effects

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- The standard challenges
  - time-dependent effects, non-linear covariate effects
- The neglected challenges
  - within-patient variability
  - informative observations times

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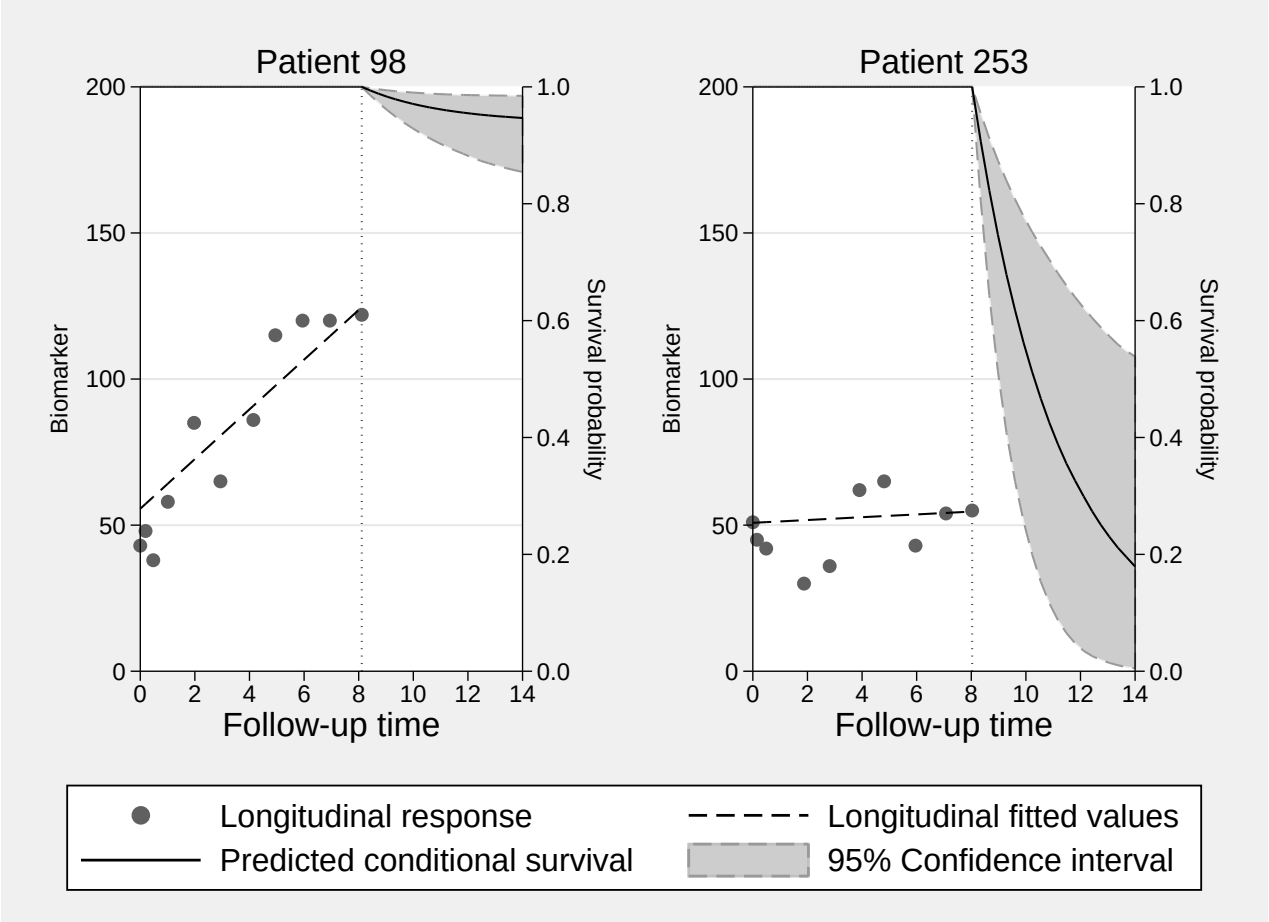
  - time-dependent effects, non-linear covariate effects
- The neglected challenges
  - within-patient variability
  - informative observations times

We need modelling frameworks that can accommodate a lot of different things

Joint longitudinal-survival models



Linking via - current value, gradient, AUC, random effects...

Joint longitudinal-survival models - extensions

- Competing risks
- Different types of outcomes
- Multiple continuous outcomes
- Delayed entry
- Recurrent events and a terminal event
- Prediction
- Many others...

Joint longitudinal-survival models - software

- stjm in Stata
- gsem in Stata
- frailtypack in R
- joineR in R
- JM and JMBayes in R
- bamlss in R
- Many others...

(My) Methods development - software

- stjm - joint longitudinal-survival models
- stmixed - multilevel survival models
- stgenreg - general parametric survival models
- ...

(My) Methods development - software

- stjm - joint longitudinal-survival models
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- ...

Each new project brings a new code base to maintain...could I make my life easier?

Mixed Effects Regression for LInear, Non-linear and user-defined models

`merlin`

The goal

- multiple outcomes of varying types
- measurement schedule can vary across outcomes
- any number of levels and random effects
- sharing and linking random effects between outcomes
- sharing functions of the expected value of other outcomes
- a reliable estimation engine
- easily extendable by the user
- ...

a unified framework for data analysis and methods development

The goal

- multiple outcomes of varying types
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a unified framework for data analysis and methods development

(I think I made my life more difficult)

(some) Maths

For a one-level model with n response variables:

$$p(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\beta}) = \prod_{i=1}^{n} p_i(y_i|\boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\beta})$$

For a two-level model:

$$p(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\beta}) = \prod_{i=1}^{n} \prod_{j=1}^{t} p_i(y_{ij}|\boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\beta})$$

(some) Maths

The log likelihood is obtained by integrating out the unobserved random effects

$$ll(\boldsymbol{\beta}) = \log \int_{\mathcal{R}^r} p(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\beta}) \phi(\boldsymbol{b}|\Sigma_{\boldsymbol{b}}) \, \mathrm{d}\boldsymbol{b}$$

we assume $\phi()$ is the multivariate normal density for $\boldsymbol{b}$, with mean vector $\mathbf{0}$ and variance-covariance matrix $\Sigma_{\boldsymbol{b}}$. We have $\Sigma_{\boldsymbol{b}}$ becoming block diagonal with further levels, with a block for each level

(some) Maths

Alternatively, exploiting conditional independence amongst level $l-1$ units, given the random effects at higher levels,

$$ll(\boldsymbol{\beta}) = \log \int \phi(\boldsymbol{b}^{(L)}|\boldsymbol{\Sigma}^{(L)}) \prod p^{(L-1)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{b}^{L}, \boldsymbol{\beta}) \, \mathrm{d}\boldsymbol{b}^{(L)}$$

where, for $l = 2, \ldots, L$

$$p^{(l)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{B}^{l+1}, \boldsymbol{\beta}) = \int \phi(\boldsymbol{b}^{(l)}|\boldsymbol{\Sigma}^{(l)}) \prod p^{(l-1)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{B}^{l}, \boldsymbol{\beta}) \, \mathrm{d}\boldsymbol{b}^{(l)}$$

Estimation challenges

- At each level, we need to integrate out our normally distributed random effects
- Generally this is done using Gauss-Hermite numerical quadrature

  `intmethod(mvaghermite | ghermite)`
- Issue with GH quadrature is it doesn't scale up well:
  - 7-point quadrature; for 1 random effect we evaluate our function at 7 points
  - 7-point quadrature; for 6 random effects, we evaluate it at $7^6 = 117,649$ points

Estimation challenges - alternatives

- An alternative is Monte Carlo integration
- Also known for its use in maximum simulated likelihood - see the special issue in the Stata Journal Vol 6 No 2
- This is a rather brute force approach, but it's usefulness is in it's simplicity

$$L(\boldsymbol{\theta}) = \int f(\boldsymbol{y}|\boldsymbol{\theta}, \boldsymbol{b})\phi(\boldsymbol{b})\partial\boldsymbol{b} = \frac{1}{m}\sum_{u=1}^{m} f(y|\theta, \boldsymbol{b}_u)$$

The important thing to note is m doesn't have to change when extra random effects are added.

Estimation challenges - alternatives

Monte Carlo integration can be improved by:

- antithetic sampling
- Halton sequences
- an adaptive procedure just like adaptive GH quadrature, resulting in an importance sampling approximation

Extensions - level-specific random effect distributions

$$ll(\boldsymbol{\theta}) = \log \int \phi_L(\boldsymbol{b}^{(L)}|\boldsymbol{\Sigma}^{(L)}) \prod p^{(L-1)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{b}^L, \boldsymbol{\beta}) \, \mathrm{d}\boldsymbol{b}^{(L)}$$

where, for $l = 2, \ldots, L$

$$p^{(l)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{B}^{l+1}, \boldsymbol{\beta}) = \int \phi_l(\boldsymbol{b}^{(l)})|\boldsymbol{\Sigma}^{(l)} \prod p^{(l-1)}(\boldsymbol{y}|\boldsymbol{x}, \boldsymbol{B}^l, \boldsymbol{\beta}) \, \mathrm{d}\boldsymbol{b}^{(l)}$$

Extensions - level-specific random effect distributions and integration techniques

- This formulation now allows us to specify different distributions at each level
- Assess robustness using the t-distribution
- Issue of which integration techniques to apply at each level
  - e.g. one random effect at level 1, many at level 2, then use AGHQ at level 3, and MCI at level 2

```
intmethod(mvaghermite mcarlo)
redistribution(normal t) df(3)
```

Standard linear predictor

The standard linear predictor for a general level model can be written as follows,

$$\eta = \boldsymbol{X}\boldsymbol{\beta} + \sum_{l=2}^{L} \boldsymbol{X}^l \boldsymbol{b}^l$$

where subscripts are omitted. We have $\boldsymbol{X}$ our vector of covariates, which could vary at any level, with associated fixed effect coefficient vector $\boldsymbol{\beta}$, and $\boldsymbol{X}^l$ the vector of covariates with random effects $\boldsymbol{b}^l$ at level l.

Extended linear predictor

$$\eta_i = g_i(E[y_i|\boldsymbol{X}, \boldsymbol{b}]) = \sum_{r=1}^{R_i} \prod_{s=1}^{S_{ir}} \psi_{irs}$$

where $g_i()$ is the link function for the ith outcome. To maintain generality, $\psi_{irs}(t)$ can take many forms, including,

$$\psi_{irs}(t) = X$$
$$\psi_{irs}(t) = \beta$$
$$\psi_{irs}(t) = b$$
$$\psi_{irs}(t) = q(t)$$
$$\psi_{irs}(t) = d_{rs}(E[y_j]), \qquad \text{where } j = 1, \ldots, k, j \neq i$$

Extended linear predictor

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And who says each outcome model can only have one complex predictor?

ssc install merlin (Stata)

Title

merlin — Mixed effects regression for linear and non-linear models

Syntax

merlin *models* [*if*] [*in*] [, *options*]

where *models* are the model specifications; see **merlin models**.

options	Description
model_description_options	fully define, along with *models*, the model to be fit
estimation_options	method used to obtain estimation results, including specifying initial values
reporting_options	reporting of estimation results

Also see **merlin postestimation** for features available after estimation.

`merlin` in Stata

- Everything I've talked about is available in the `merlin` package in Stata
- `merlin` has many extensions, such as
  - Alternative models, such as spline based survival models
  - Extending sharing between outcomes, motivated by joint modelling
  - User-defined likelihood functions
  - Other things...

`merlin` in R

- is catching up (slowly)
- a first version is on CRAN

Distributional choices

- Gaussian, Poisson, binomial, beta, negative binomial, ordinal (logit or probit link)
- exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, Royston-Parmar, splines on log hazard scale
- non-linear outcome models
- user-defined hazard functions
- many (many) more to add...

An example

- we're going to fit 15 models
- each of them is applied to the same dataset
- some of them can be considered *new* models
- we can fit all of them with a single line of code (ok, it may get quite long...)

- data from 312 patients with PBC collected at the Mayo Clinic 1974-1984 (Murtaugh et al. (1994))
- 158 randomised to receive D-penicillamine and 154 to placebo
- survival outcome is all-cause death, with 140 events observed
    - we're going to pretend we have competing causes of death - cancer and other causes
- 1,945 measurements of serum bilirubin, among other things

data

id	time	logb	prothr~n	trt	stime	cancer	other
1	0	2.674149	12.2	D-penicil	1.09517	1	0
1	.525682	3.058707	11.2	D-penicil	.	.	.
2	0	.0953102	10.6	D-penicil	14.1523	0	1
2	.498302	-.2231435	11	D-penicil	.	.	.
2	.999343	0	11.6	D-penicil	.	.	.
2	2.10273	.6418539	10.6	D-penicil	.	.	.
2	4.90089	.9555114	11.3	D-penicil	.	.	.
2	5.88928	1.280934	11.5	D-penicil	.	.	.
2	6.88588	1.435084	.	D-penicil	.	.	.
2	7.8907	1.280934	.	D-penicil	.	.	.
2	8.83255	1.526056	.	D-penicil	.	.	.

a model

```
merlin (logb                                /// log serum bilirubin
               time                         /// covariate
               ,                            /// options
               family(gaussian)             /// distribution
       )
```

a model

```
merlin (logb                        /// log serum bilirubin
               time                 /// covariate
               time#trt             /// interaction
               ,                    /// options
               family(gaussian)     /// distribution
       )                            ///
```

a model

```
merlin (logb                                /// log serum bilirubin
                time                        /// covariate
                time#trt                    /// interaction
                M1[id]@1                    /// random intercept
                ,                           /// options
                family(gaussian)            /// distribution
        )                                   ///
```

a model

```
merlin (logb                                /// log serum bilirubin
                time                        /// covariate
                time#trt                    /// interaction
                M1[id]@1                    /// random intercept
                time#M2[id]@1               /// random slope
                ,                           /// options
                family(gaussian)            /// distribution
        )
```

a model

```
merlin (logb                                /// log serum bilirubin
               time                         /// covariate
               time#trt                     /// interaction
               M1[id]@1                     /// random intercept
               time#M2[id]@1                /// random slope
               ,                            /// options
               family(gaussian)             /// distribution
       )                                    ///
       (pro                                 /// prothrombin index
               rcs(time, df(3))             /// covariate
               , family(gamma)              /// distribution
       )                                    ///
```

a model

```
merlin (logb                                /// log serum bilirubin
               time                         /// covariate
               time#trt                     /// interaction
               M1[id]@1                     /// random intercept
               time#M2[id]@1                /// random slope
               ,                            /// options
               family(gaussian)             /// distribution
       )                                    ///
       (pro                                 /// prothrombin index
               rcs(time, df(3))             /// covariate
               M3[id]@1                     /// random effect
               , family(gamma)              /// distribution
       )                                    ///
```

a model

```
merlin (logb                                    /// log serum bilirubin
               time                             /// covariate
               time#trt                         /// interaction
               M1[id]@1                         /// random intercept
               time#M2[id]@1                    /// random slope
               ,                                /// options
               family(gaussian)                 /// distribution
       )                                        ///
       (pro                                     /// prothrombin index
               rcs(time, df(3))                 /// covariate
               M3[id]@1                         /// random effect
               , family(gamma)                  /// distribution
       )                                        ///
       ,                                        /// main options
       covariance(unstructured)                 //  vcv
```

a model

```
merlin (logb                                    /// log serum bilirubin
               time                             /// covariate
               time#trt                         /// interaction
               M1[id]@1                         /// random intercept
               time#M2[id]@1                    /// random slope
               ,                                /// options
               family(gaussian)                 /// distribution
       )                                        ///
       (pro                                     /// prothrombin index
               rcs(time, df(3))                 /// covariate
               M3[id]@1                         /// random effect
               , family(gamma)                  /// distribution
       )                                        ///
       ,                                        /// main options
       covariance(unstructured)                 /// vcv
       redistribution(t) df(5)                  //  re dist.
```

a model

```
merlin (logb                                /// log serum bilirubin
               time                         /// covariate
               time#trt                     /// interaction
               M1[id]@1                     /// random intercept
               time#M2[id]@1                /// random slope
               ,                            /// options
               family(gaussian)             /// distribution
       )                                    ///
       (pro                                 /// prothrombin index
               rcs(time, df(3))             /// covariate
               M3[id]@1                     /// random effect
               , family(gamma)              /// distribution
       )                                    ///
       (stime  trt                          /// response + covariate
              , family(rp, df(3)            /// distribution
                       failure(other))      /// event indicator
       )                                    ///
       ,                                    /// main options
       covariance(unstructured)             /// vcv
       redistribution(t) df(5)              //  re dist.
```

a model

```
merlin (logb                                    /// log serum bilirubin
               time                             /// covariate
               time#trt                         /// interaction
               M1[id]@1                         /// random intercept
               time#M2[id]@1                    /// random slope
               ,                                /// options
               family(gaussian)                 /// distribution
       )                                        ///
       (pro                                     /// prothrombin index
               rcs(time, df(3))                 /// covariate
               M3[id]@1                         /// random effect
               , family(gamma)                  /// distribution
       )                                        ///
       (stime  trt                              /// response + covariate
               dEV[logb] EV[pro]                /// associations
               , family(rp, df(3)               /// distribution
                       failure(other))          /// event indicator
       )                                        ///
       ,                                        /// main options
       covariance(unstructured)                 /// vcv
       redistribution(t) df(5)                  //  re dist.
```

a model

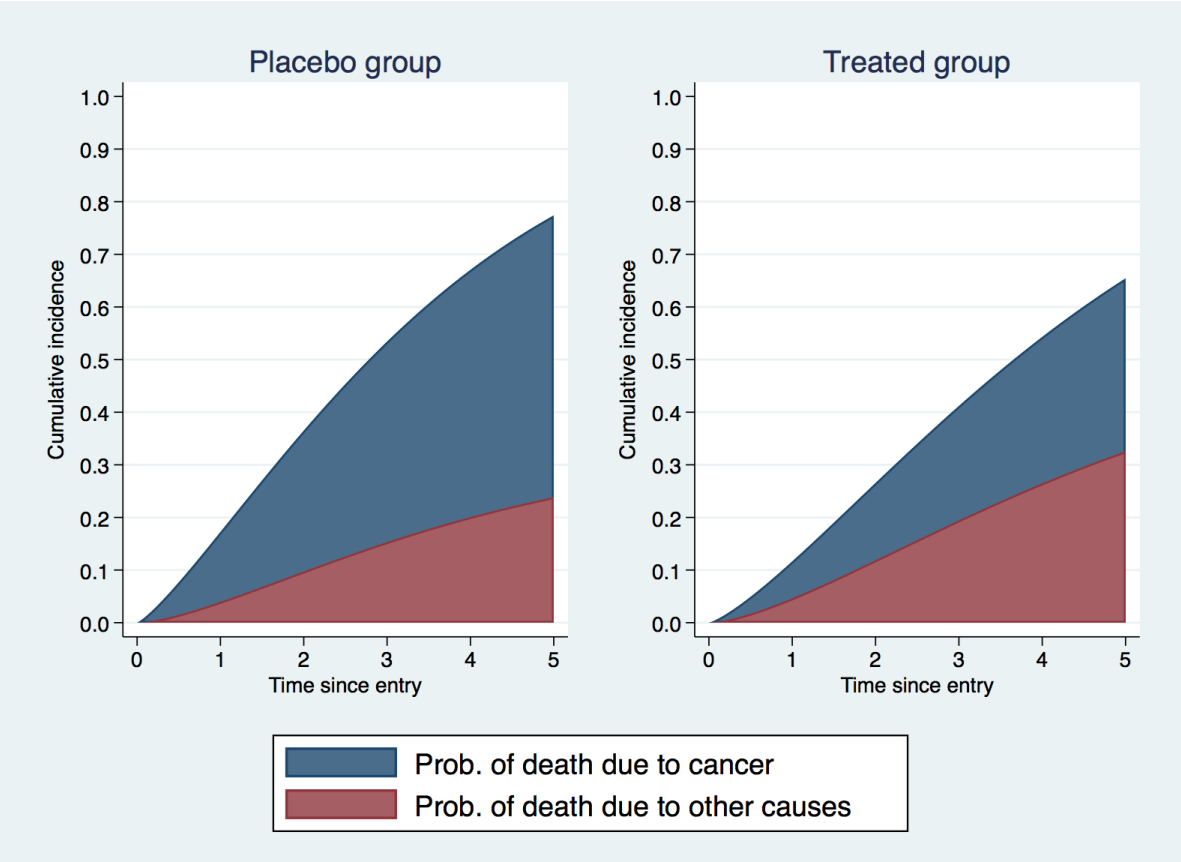
```
merlin (logb                                    /// log serum bilirubin
               time                             /// covariate
               time#trt                         /// interaction
               M1[id]@1                         /// random intercept
               time#M2[id]@1                    /// random slope
               ,                                /// options
               family(gaussian)                 /// distribution
       )                                        ///
       (pro                                     /// prothrombin index
               rcs(time, df(3))                 /// covariate
               M3[id]@1                         /// random effect
               , family(gamma)                  /// distribution
       )                                        ///
       (stime  trt                              /// response + covariate
               trt#fp(stime, power(0))          /// tde
               dEV[logb] EV[pro]                /// associations
               , family(rp, df(3)               /// distribution
                        failure(other))         /// event indicator
       )                                        ///
       ,                                        /// main options
       covariance(unstructured)                 /// vcv
       redistribution(t) df(5)                  //  re dist.
```

a model

```
merlin (logb time time#trt M1[id]@1          /// model 1
               time#M2[id]@1 ,               ///
               family(gaussian)              ///
       )                                     ///
       (pro  rcs(time, df(3)) M3[id]@1       /// model 2
               , family(gamma)               ///
       )                                     ///
       (stime  trt                           ///
               trt#fp(stime, power(0))       /// model 3 - cause 1
               dEV[logb] EV[pro]             /// tde
               , family(rp, df(3)            /// distribution
                        failure(other))      /// event indicator
       )                                     ///
       (stime  trt                           /// model 4 - cause 2
               trt#rcs(stime, df(3) log)     /// tde
               EV[logb] iEV[pro]             /// associations
               , family(weibull,             /// distribution
                        failure(cancer))     /// event indicator
       )                                     ///
       ,                                     ///
       covariance(unstructured)
```

predictions

```
predict cif1, cif marginal outcome(3) at(trt 0)
predict cif1, cif marginal outcome(4) at(trt 0)
```



a user-defined model

```
real matrix gauss_logl(gml)
{
      y          = merlin_util_depvar(gml)          // dep. var.
      linpred    = merlin_util_xzb(gml)             // lin. pred.
      sdre       = exp(merlin_util_ap(gml,1))       // anc. param.
      return(lnnormalden(y,linpred,sdre))          // logl
}

merlin (logb ... , family(user, llfunction(gauss_logl) nap(1)))
        ...
        ...
        ...
```

a user-defined model

```
real matrix gauss_logl(gml)
{
      y         = merlin_util_depvar(gml)          // dep. var.
      linpred   = merlin_util_xzb(gml)             // lin. pred.
      sdre      = exp(merlin_util_xzb_mod(gml,2)) // anc. param.
      return(lnnormalden(y,linpred,sdre))        // logl
}

merlin (logb ...     , family(user, llfunction(gauss_logl)))
       (age M1[id]@1, family(null))
       ...
       ...
```

a user-defined non-linear model

```
webuse orange, clear
menl circumf = (b1+U1[tree])/(1+exp(-(age-b2)/b3))

mata:
real matrix logl(transmorphic gml)
{
    y    = merlin_util_depvar(gml)

    b1   = merlin_util_xzb(gml)
    b2   = merlin_util_xzb_mod(gml,2)
    b3   = merlin_util_xzb_mod(gml,3)

    sdre = exp(merlin_util_ap(gml,1))

    xb   = b1 :/ (1 :+ exp(-b2 :/ b3))

    return(lnnormalden(y,xb,sdre))
}
end

merlin (circumf M1[tree]@1, family(user, llf(logl) nap(1)))
       ( age@1             , family(null))
       (                   , family(null))
```

Things I didn't show

- random effects at arbitrary levels - `M4[centre>id]@1`
- B-splines - `bs(time, df(3) order(4))`
- `d2EV[]`, `?XB[]`
- `linterval(varname)` - interval censoring
- `ltruncated(varname)` - left-truncation
- 9 (so far) other inbuilt families, e.g. `beta`, `ologit`
- `bhazard(varname)` - relative survival
- `mf(func_name)` - user-defined element function

the family

- `merlin`'s syntax is not simple
- we can develop more user-friendly wrapper functions to allow a simpler syntax for special cases
- `merlin`'s minions...
  - `stmixed` (`excalibur`) for multilevel survival analysis (now published in Stata Journal)
  - `predictms2` (`galahad`) - multi-state survival analysis
  - TBC (`lancelot`) - meta-analysis
  - TBC (`arthur`) - to be revealed next!

a surprise

Two useful features of `merlin` are:

- `EV[depvar/#]` element type
  - implemented for their use in joint longitudinal-survival models
- `family(null)`
  - implemented for use with user-defined models

their combination gives merlin some new capabilities

a surprise

```
merlin (y x1 x2 EV[2] EV[3], family(bernoulli) link(logit))
       (x1 x2, family(null) link(logit))
       (x1 x2, family(null) link(logit))
```

any idea what this is?

a surprise

```
merlin (y x1 x2 EV[2] EV[3], family(bernoulli) link(logit))
       (x1 x2, family(null) link(logit))
       (x1 x2, family(null) link(logit))
```

any idea what this is?

It's an artificial neural network!

Title

neuralnet — fit an artificial neural network

Syntax

neuralnet [*varlist*] , *options*

where *varlist* defines any inputs to the network.

options	Description
output#(*depvar*, *op_opts***)**	output model specification; see details
hlayers(*#***)**	number of hidden layers in the network
hlink(*link_list***)**	link functions for each hidden layer to the layer above
hnodes(*numlist***)**	number of nodes per hidden layer
penalty(*pen_func***)**	penalty function; **lasso** or **ridge**
lambda(*#***)**	penalty parameter value; default 0.1
nostandardise	do not standardise input variables to [0,1]
loss	minimise the loss function instead of maximising the log-likelihood
showmerlin	displays the **merlin** command used in estimating the network
merlin_opts	options to pass to **merlin**

output options	Description
family(*fam_spec***)**	distributional family for the output/response, see **merlin families**
link(*type***)**	link function for the response model

a surprise

```
merlin (y x1 x2 EV[2] EV[3], family(bernoulli) link(logit))
       (x1 x2, family(null) link(logit))
       (x1 x2, family(null) link(logit))

neuralnet x1 x2, output1(y, family(bernoulli) link(logit))
                 hlayers(1) hlink(logit) hnodes(2)
                 penalty(ridge) lambda(1e-07)
```

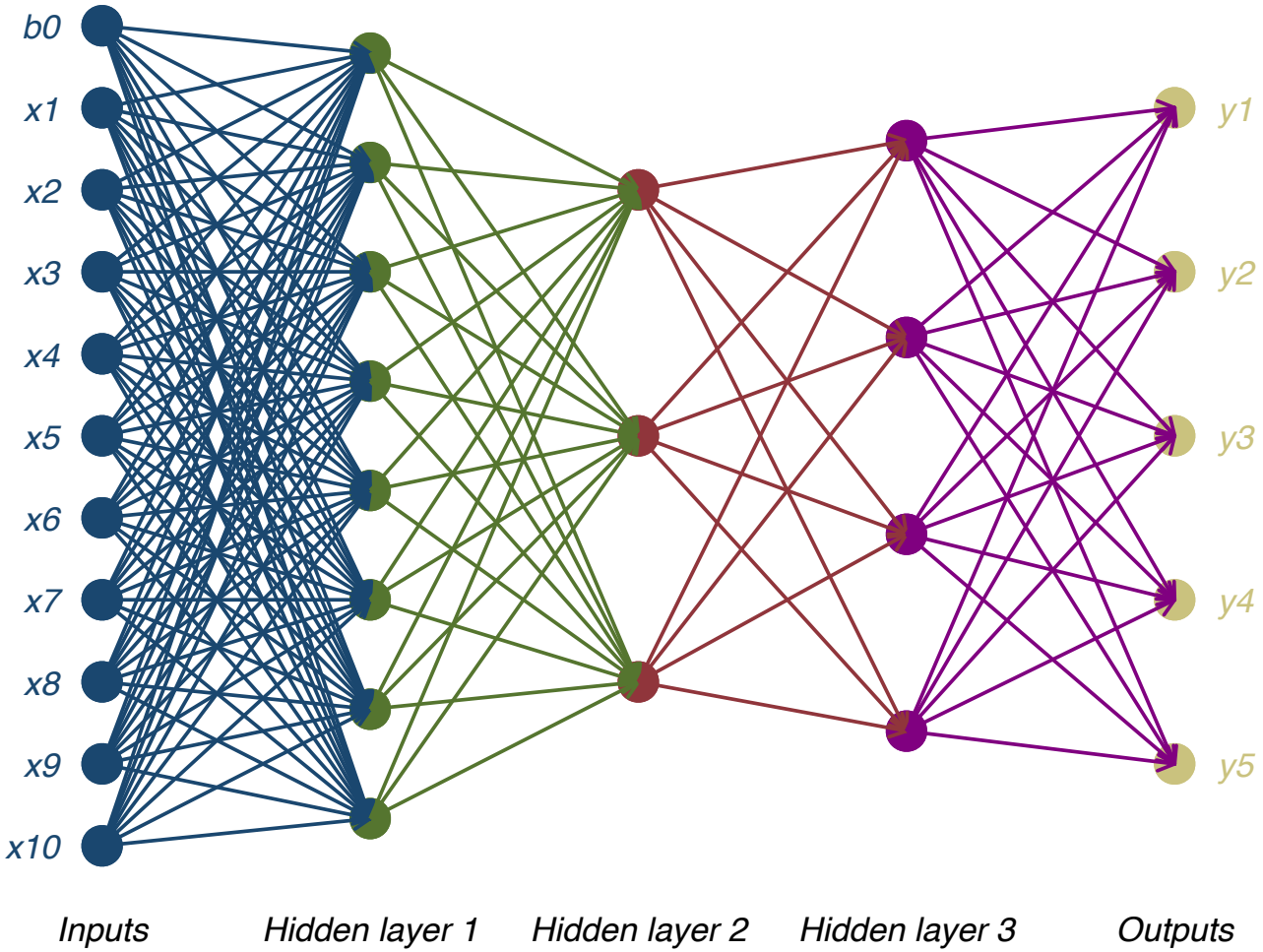
a surprise

```
merlin (y x1_nn x2_nn EV[4] EV[5] EV[6]
                              , family(bernoulli) link(logit))
       (x1_nn x2_nn, family(null) link(atanh))
       (x1_nn x2_nn, family(null) link(atanh))
       (EV[2] EV[3], family(null) link(atanh))
       (EV[2] EV[3], family(null) link(atanh))
       (EV[2] EV[3], family(null) link(atanh))

neuralnet x1 x2, output1(y, family(bernoulli) link(logit))
                 hlink(atanh) hlayers(2) hnodes(2 3)
                 penalty(lasso) lambda(1e-07)
```

```
. nnplot , inputs(10) outputs(5) hlayers(3) hnodes(8 3 4)
```

Artificial neural network



From my website - I'm now a data scientist!

Interests

- Survival Analysis
- Multilevel Models
- Joint Modelling
- Machine Learning
- Software Development

The future

- `merlin` can do a lot of things, hopefully in a usable way
- `merlin` is easily extended
- Dynamic risk prediction - predictions are a key focus of the `merlin` engine
- It's general, and hence it can be slow(er)

www.mjcrowther.co.uk/software/merlin

Papers

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