Mixed effects model for comparing treatments that alter length of life in the *C. elegans* model

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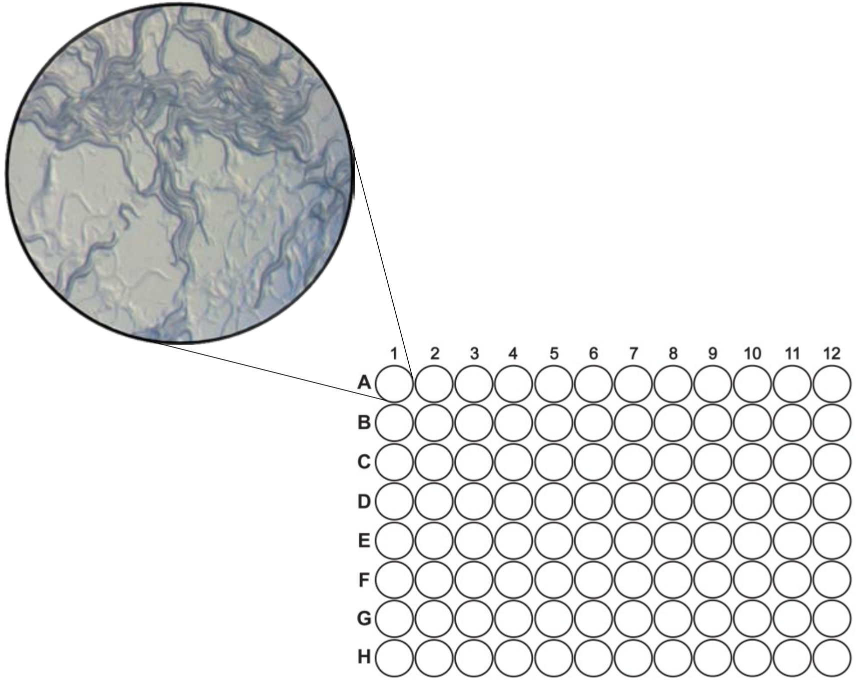
C. elegans

- *Caenorhabditis elegans*
  - Free-living, non-parasitic, transparent nematode
  - Model system commonly used in laboratory studies
    - Time- and cost-efficient
  - Important for translational studies
    - Genome similar to humans

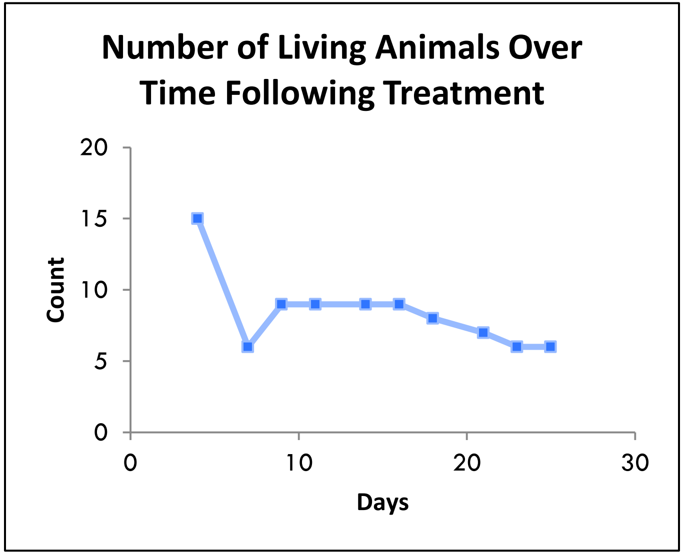
Setup



- Aging / lifespan studies
  - 96-well plate
  - Treatments and replicates arranged in rows and columns
  - Each well contains numerous specimens
  - Record counts of number alive in each well at specified time points

Issues

- Goal is to estimate effect of treatments on lifespan
- Issues affecting analytic plan
  - Cannot track survival times of individuals
  - Animals may reproduce
    - Cannot differentiate between existing animals and newly birthed animals
    - Can only measure counts of live animals at each time point
  - Important for translational studies
- Traditional survival analysis not appropriate



Alternative

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = x_{ij}\beta, \qquad i = 1, \ldots, N, \qquad j = 1, \ldots, T$$

- Suggested analysis
  - Generalized linear model (logit model)
  - Models the natural log of the odds of being alive
- Model definition
  - N is number of experimental units (wells)
  - T is number of time points at which experimental units are observed
  - π_{ij} is the probability of being alive in well i at time j
  - x_{ij} is the p-dimensional row vector of covariates for well i at time j
  - β is p-dimensional column vector of fixed effects parameters

Illustration

- Wish to estimate the probability of survival of *C. elegans* following exposure to various concentrations of the insecticide Imidacloprid
  - Four concentrations are investigated
- Experimental setup
  - Groups of worms are added to wells
  - Each well contains a solution of one of the four insecticide concentrations
  - Starting counts of worms are similar, but are not the same in every well
    - Justification for use of proportions rather than counts
  - Number of living worms in each well is observed and recorded repeatedly at pre-determined days

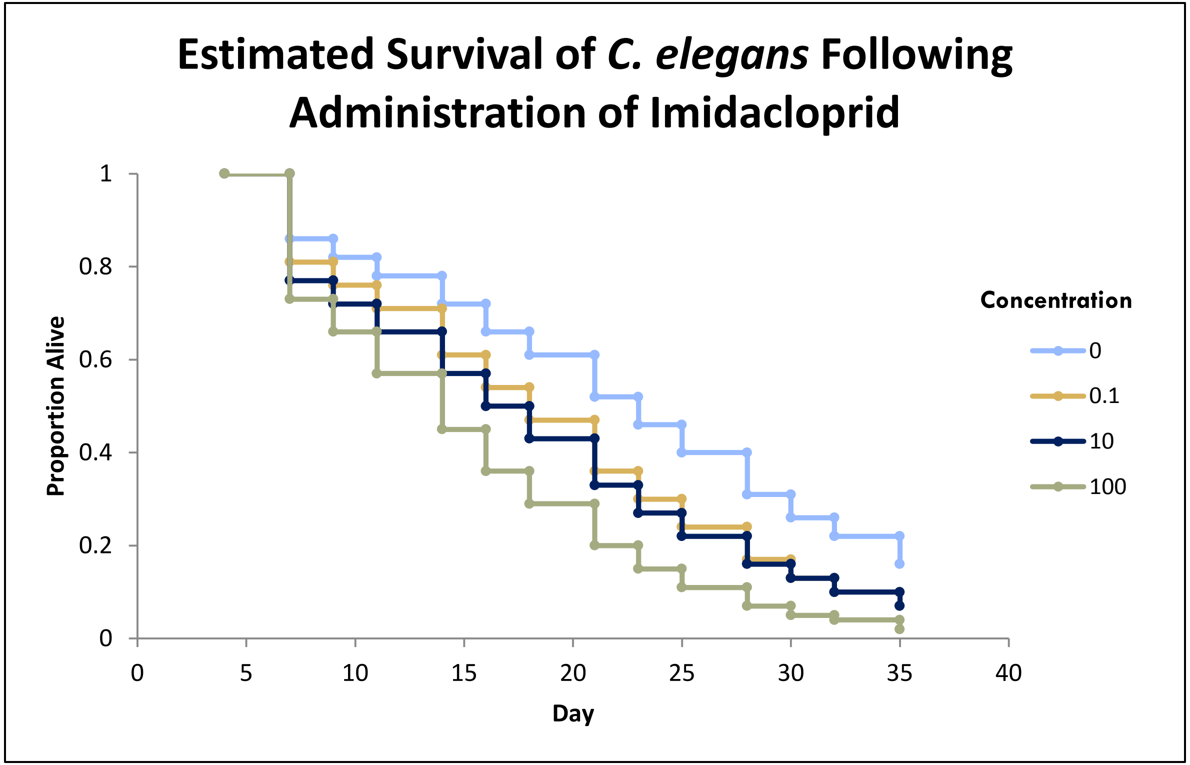
Illustration

$$\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = x_{ij}\beta, \qquad i = 1, \dots, N, \qquad j = 1, \dots, T$$

- Model definition
  - $N = 96,\ T = 14$
  - $x_{ij} = (1 \quad g_i \quad t_j \quad g_i * t_j)$
    - First column represents intercept
    - g_i is indicator variable for treatment group of well i
    - t_j is time point j
  - $\beta = (\beta_0 \quad \beta_g \quad \beta_t \quad \beta_{g*t})'$

- Logit model fit using SAS PROC GLIMMIX
  - Parameter estimates output from this models can be used for calculating surrogates of estimated survival probabilities
    - $\hat{\pi}_{ij} = \frac{\exp(x_{ij}\hat{\beta})}{1+\exp(x_{ij}\hat{\beta})}$

Graph of Results



Conclusion

- Traditional survival analysis is not appropriate when:
  - Data are observed at group-level
  - Individuals can not be tracked
- Use generalized linear model for this setting
  - Observed response is proportion of living subjects over time
  - Logit link function models the natual log of the odds of being alive
  - Avoid need to make assumptions of traditional survival analysis
- Estimated binomial probabilities can be used as surrogates for estimated survival probabilities

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