Statistical Inference in a Two-Compartment Model for Hematopoiesis

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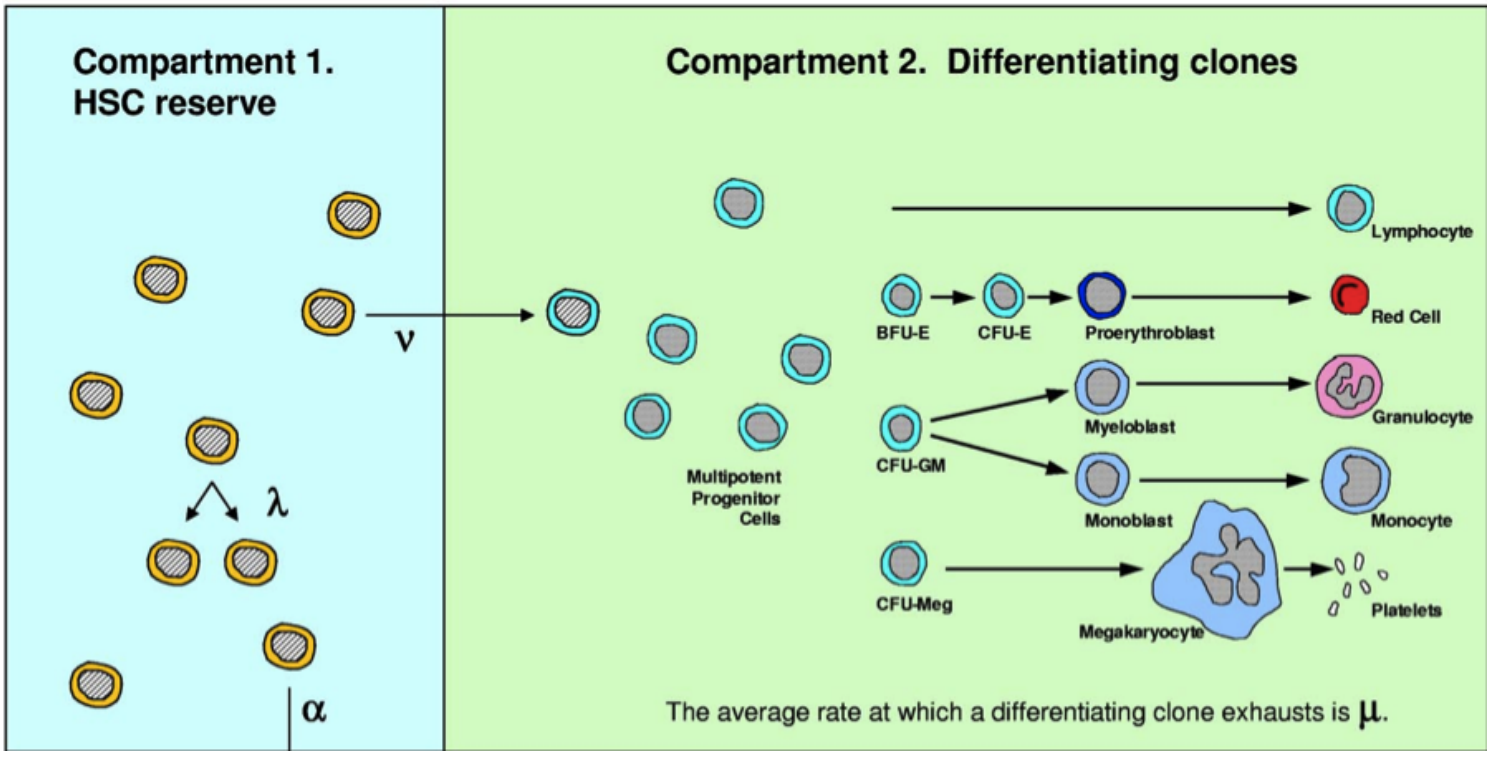
What is Hematopoiesis?

Hematopoeisis: Process of specialization of stem cells into mature blood cells

- HSCs differentiate (specialize) into progenitor cells: multi-stage process
- Progenitor cells further differentiate to white/red blood cells, platelets, etc. This is well-studied.
- Little is known about early stages: unidentifiability of HSCs

A Stochastic Model

- First birth-death model for hematopoeisis: Till et al, 1963
- Experimentally justified, refined over several studies
- Current paper analyzes hidden two-compartment model



A Stochastic Model

Goal: Develop inferential tools for this problem, and for a class of stochastic population processes

Statistical motivation: Tools for inference in a useful class of models. Hidden compartmental processes include

- SIR models
- Spread of malaria in human host (Gravenor 1998)

Application: Clinical and biological importance

- Cancer therapy: stem cell transplantation
- Gene therapy
- "A remarkable cell renewal process"; close to 1 trillion cells per day supported by HSCs (M. Ogawa)

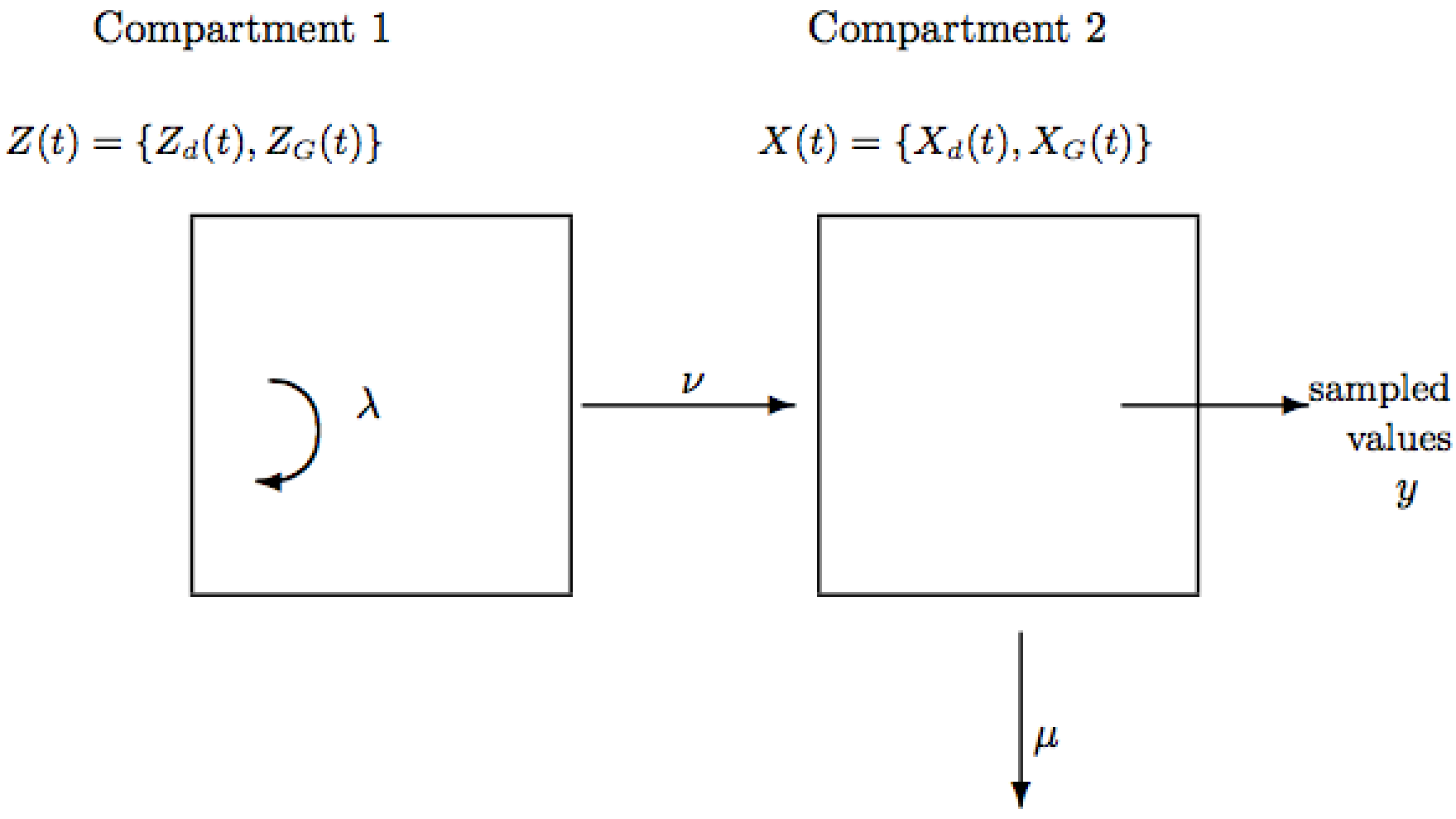
Experimental design

Female safari cat study

- Distinct G6PD phenotype expressed as d or G
- Retained after replication/differentiation; neutral
- Provides binary marker of each cell and its clones

Observing proportion of, say d, allows us to "track" HSC behavior

The model


Compartment 1
Compartment 2
$Z(t) = \{Z_d(t), Z_G(t)\}$
$X(t) = \{X_d(t), X_G(t)\}$
λ
ν
sampled values y
μ

The model

Simple continuous time, discrete state process:

- Compartment 1 is a linear birth-death (BD) process
- Compartment 2 is a non-homogeneous immigration-death process
- Inference: rates λ, ν, μ

Likelihood: $L(\lambda, \nu, \mu) \propto \lambda^{B_T} \nu^{E_T} \mu^{D_T} \exp(-(\lambda + \nu) S_T^z - \mu S_T^x)$

- $B_T =$ births, $E_T =$ emigrations, $D_T =$ deaths, $S_T^i =$ total time in i
- MLEs available: $\hat{\lambda} = B_T / S_T^z$, $\hat{\nu} = E_T / S_T^Z$, $\hat{\mu} = D_T / S_T^x$; nice asymptotic properties

Difficulty: Partial Observations

We only have sampled values from the second compartment: $Y(t)$, the total cells marked d, is a hidden Markov process

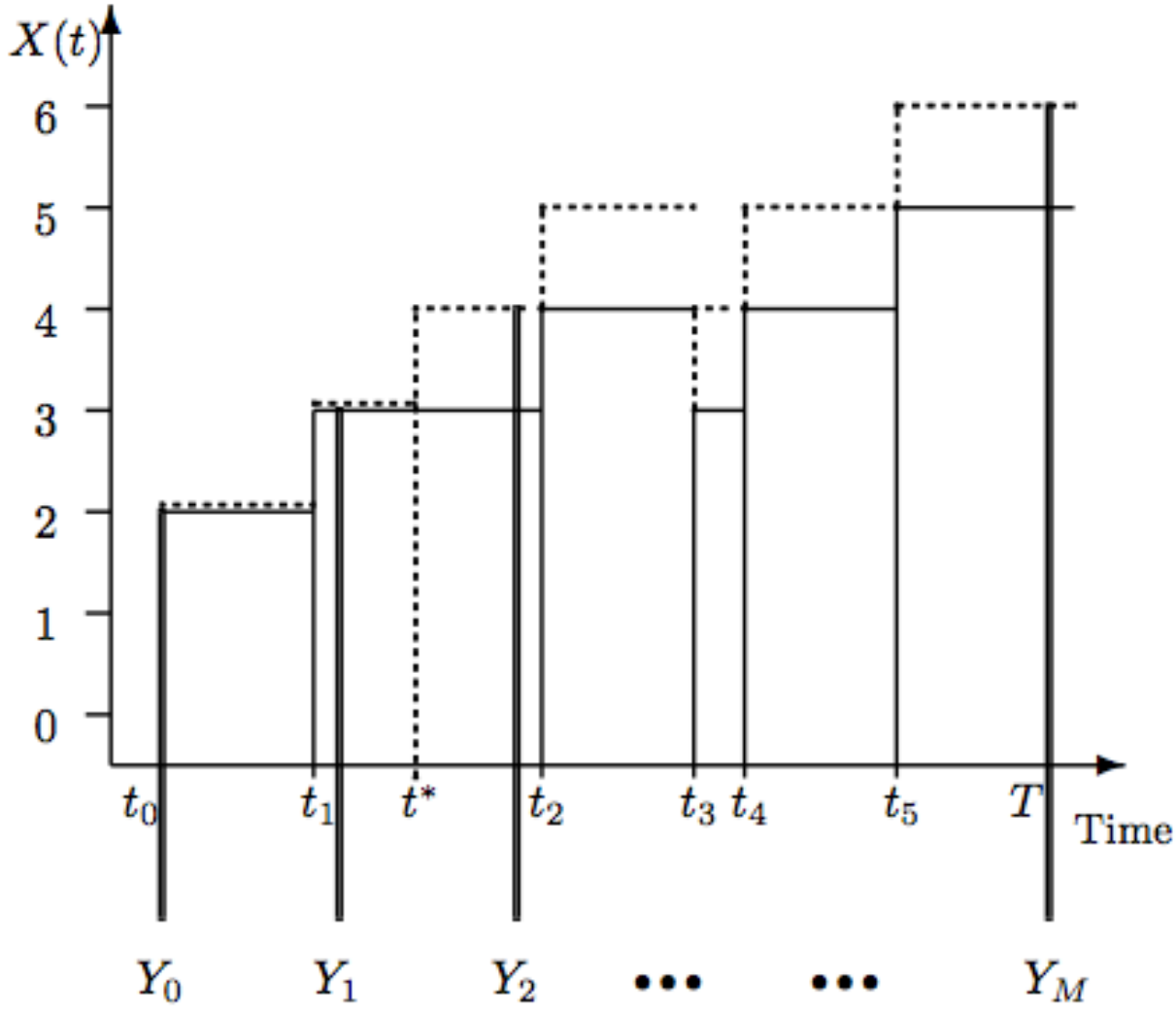
$$[Y(t)|(x(t), z(t))] \sim Binom(N_t, \frac{x_d(t)}{x_d(t) + x_G(t)})$$

- Distribution of this binomial proportion mathematically difficult
- Exact likelihood methods infeasible
- No successful attempts in obtaining transition probabilities

Other Approaches

- Abkowitz (1996): vary parameters and simulate realizations: compare simulations to true data
- Catlin (1997): normal approximation of transition probabilities
- Golinelli (2006): Bayesian inference via RJMCMC
  - Integrate over paths between discrete observations
  - Most precise estimates and effective use of data at computational cost

Other Approaches



Current Method

Estimating equation approach

- Calculate moments of process by solving Kolmogorov forward equation
- Create estimating function relating these expressions and data
  - Method of moments cannot be used directly: differing population sizes over realizations at given time
- Solve using nonlinear least squares

Discussion

- Simulations starting with estimated rates close to observed data
- Parameter estimates very similar to results from other studies
- Minor discrepancies: theoretical and simulated errors
- Advantages: not restricted to large population sizes
  - Accurate parameter estimates without much computational cost
  - Provides standard error estimates
- Drawbacks: does not utilize all data efficiently
  - Dependent on number of realizations
  - Biological shortcomings

Discussion

Closing remarks: While not able to make as efficient use of data as stochastic integration methods, provides a more "elegant" solution that is accurate and applicable when MCMC methods become infeasible.

Studying hematopoiesis via two-compartment stochastic model has provided much insight to understanding the complex behavior of HSCs.

The Kolmogorov Forward Equation

From Bailey (1964), we can obtain a PDE for CGF of multi-dimensional Markov processes as

$$\frac{dK(\theta_1, \theta_2; t)}{dt} = \sum_{j,k} (e^{j\theta_1 + k\theta_2} - 1) f_{jk}(\frac{d}{d\theta_1}, \frac{d}{d\theta_2}) K(\theta_1, \theta_2; t)$$

In our case, the f_{jk} are simple rates:

$f_{1,0} = \lambda x$, $f_{-1,1} = \nu x$, and $f_{0,1} = \mu y$.

Thus,

$$\frac{dK(\theta_1, \theta_2; t)}{dt} = [\lambda(e_1^{\theta} - 1) + \nu(e^{-\theta_1 + \theta_2} - 1)] \frac{dK}{d\theta_1} + \mu(e^{-\theta_2} - 1) \frac{dK}{d\theta_2}$$

Getting the cumulants

- Since CGF $=$ log(MGF), the first and second cumulants κ_1, κ_2 yield mean, variance
- We can obtain a system of ODE's for cumulants by expanding the CGF, taking partial derivatives, and equating coefficients of products of θ_i
- Successively solving yields desired moments

Getting the cumulants: example

Consider the simple case of a linear birth-death process:

$$\frac{dK}{dt} = [\lambda(e^{\theta} - 1) + \mu(e^{-\theta} - 1)]\frac{dK}{d\theta}$$

The cumulant generating function

$$K(\theta) = \kappa_1\theta + \kappa_2\theta^2/2! + \kappa_3\theta^3/3! + \ldots$$

Differentiating this with respect to θ and t yields

$$\frac{d^2K}{dtd\theta} = \frac{d\kappa_1}{dt} + \theta\frac{d\kappa_2}{dt} + \ldots$$

To get κ_1...

Getting the cumulants: example

- Differentiate forward equation with respect to θ:

$$\frac{d^2K}{dtd\theta} = (\lambda e^{\theta} - \mu e^{-\theta})\frac{dK}{d\theta} + [\lambda(e^{\theta} - 1) + \mu(e^{-\theta} - 1)]\frac{d^2K}{d\theta^2}$$

- Evaluate at $\theta = 0$ in both expressions and equate:

$$\frac{d\kappa_1}{dt} = (\lambda - \mu)\kappa_1$$

- We arrive at an ODE! In this case, it is easily solvable:

$$\kappa_1 = e^{(\lambda-\mu)t}$$

Getting the cumulants: example

Similarly, κ_2 is obtained by taking $\frac{d^2}{d\theta^2}$: we obtain $\frac{d\kappa_2}{dt} = (\lambda+\mu)\kappa_1 + 2(\lambda-\mu)\kappa_2$, which has solution

$$\kappa_2 = \frac{\lambda+\mu}{\lambda-\mu} e^{(\lambda-\mu)t}\left(e^{(\lambda-\mu)t} - 1\right)$$

- These solutions actually relevant: recall, reserve compartment is a linear birth-death process
- Analogous expansion of our bivariate CGF: system of five ODE's; closed forms for means and variances available

Deriving the estimating equation: setup

- Particle independence: treat the process beginning with r_0 cells as a sum of r_0 independent processes beginning with 1 cell: justifies application of CLT.
- Aymptotics of observed proportion $P(t) := \frac{x_d(t)}{x_d(t)+x_G(t)}$ obtained using the moments calculated and applying delta method:

$$\sqrt{(r_0)}(P(t) - 1/2) \to N[0, \sigma^2_{P_1(t)}]$$

- $\sigma^2_{P_1(t)}$ is a nasty expression: it is important that it is a nonlinear function of three variables (λ, ν, μ)

Deriving the estimating equation: expectation and variance

Remember, we observe the proportion $P(t)$ in the second compartment to estimate the true proportion $Y(t)/n(t)$: using iterated expectations/variances by conditioning on $P(t)$,

- $E(\frac{Y(t)}{n(t)}) = 1/2$
- $Var(\frac{Y(t)}{n(t)}) = (1 - \frac{1}{n(t)})\sigma^2_{P(t)} + \frac{1}{4n(t)}$
- Across realizations given a time t, inference can be based on the sample variance for (y_i, n_i) at realizations (cats) $i = 1, \ldots, m$.

Almost there...

Thus, we cook up a function

$$g_t(\frac{y_i}{n_i}) = (\frac{y_i}{n_i} - \frac{1}{2}) / \sqrt{(1 - \frac{1}{n_i}\sigma^2_{P(t)} + \frac{1}{4n_i}}$$

constructed to have variance equal to 1.

Setting $\sum_{i=1}^{m} g_t^2(\frac{y_i}{n_i})/m = 1$, we arrive at the estimating function

$$\Psi_{j,m_j}(\theta) = \frac{1}{m_j} \sum_{i=1}^{m_j} \frac{(\frac{y_i}{n_i} - \frac{1}{2})^2}{(1 - \frac{1}{n_i}\sigma^2_{P(t_j)} + \frac{1}{4n_i})} - 1 = 0$$

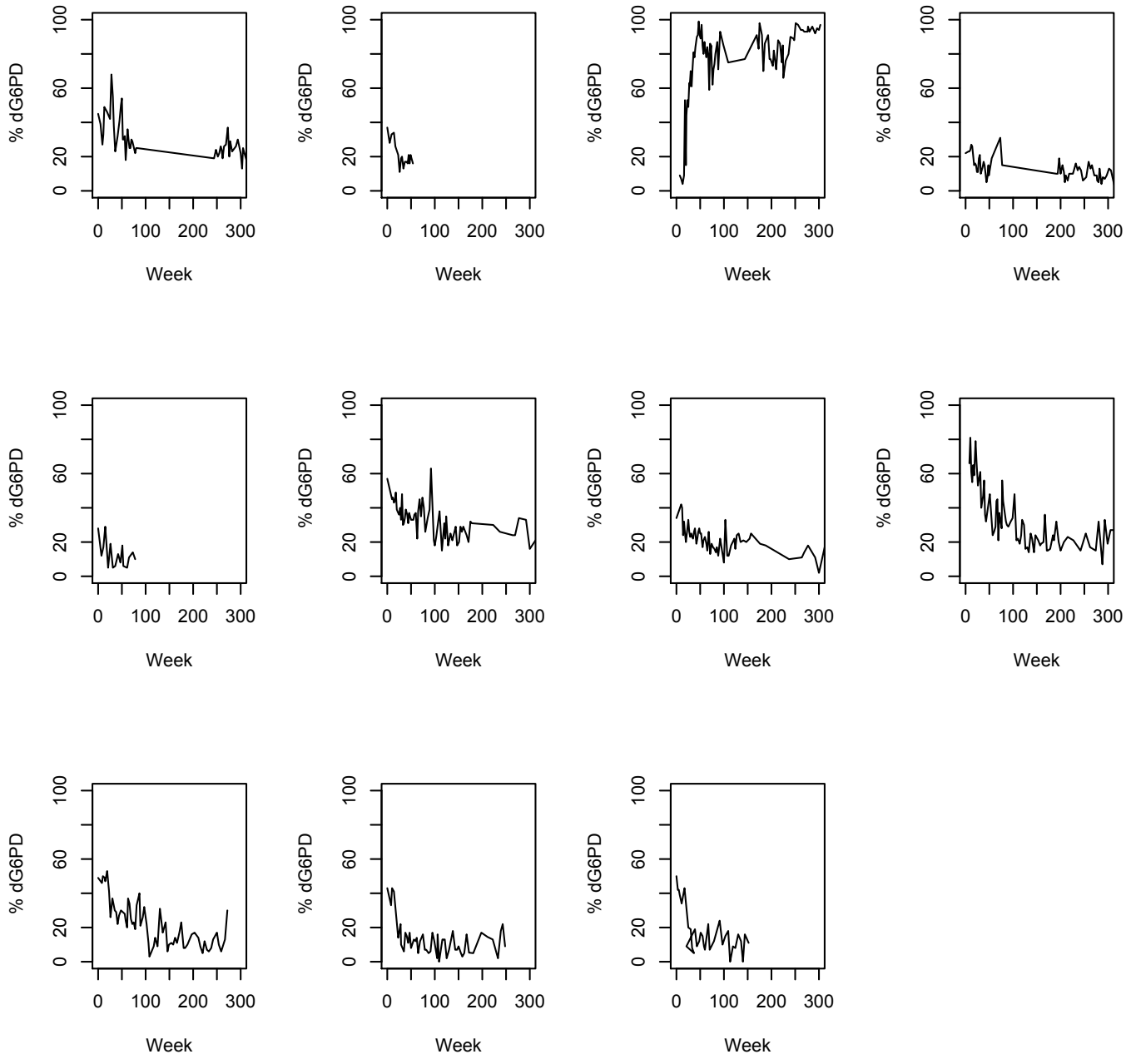
where $\theta = (\lambda, \nu, \mu)$

Solving the equation

- Observations from at least three times t_j allows us to solve for the three unknowns.
- Nonlinear system: numerical solution
- Asymptotic variance of estimates: use modified Huber's M Theorem (maybe next time...)
- Next, let's try it out on some data

Missing data (seriously)

Missing data (seriously)



Solving the equation in R

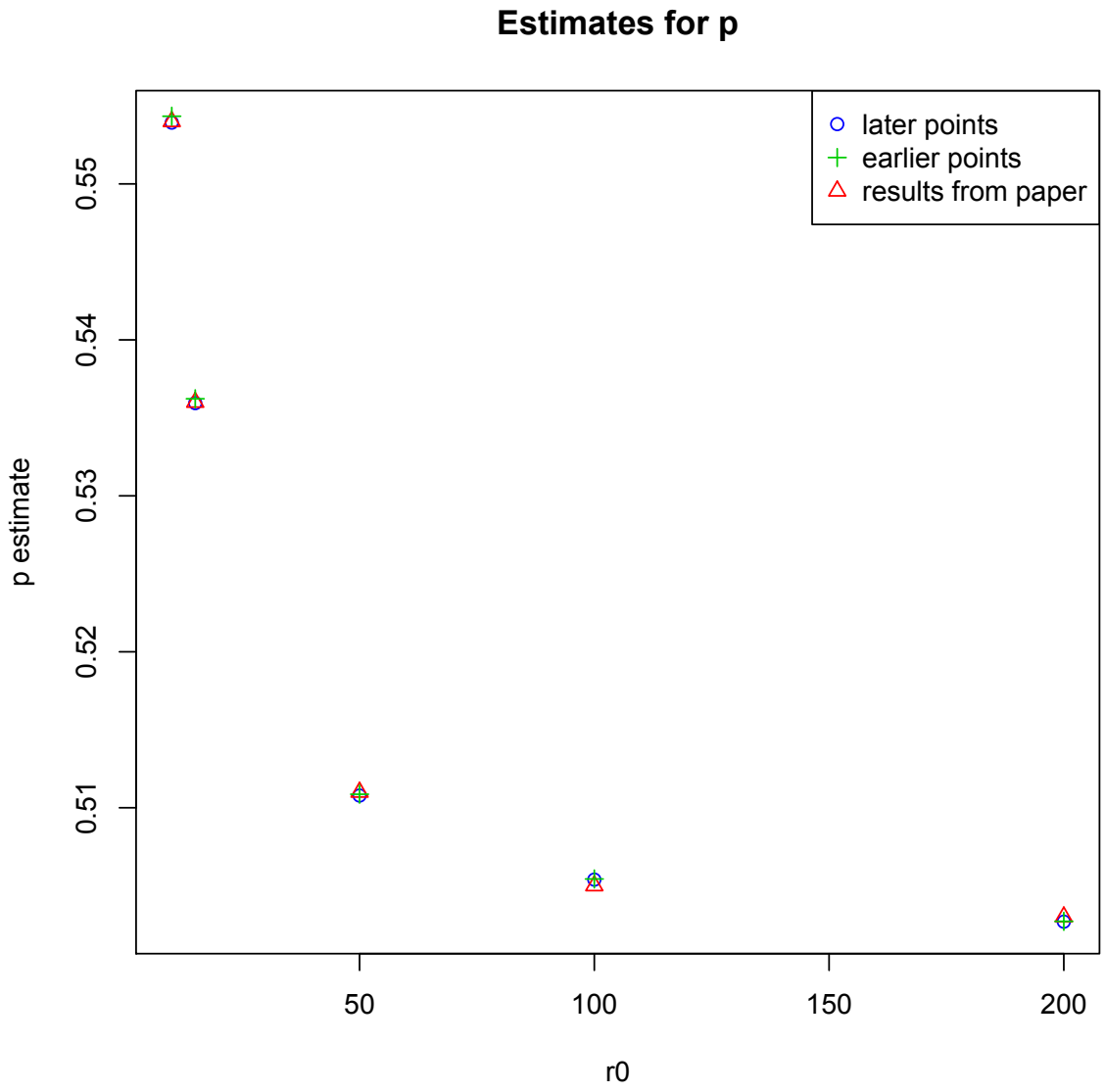
- Because observations are sparse, we choose weeks 15, 51, and 267, and group together observations within 3 week intervals
- 11, 11, and 6 cats were available, respectively
- Solution using rootSolve, BB packages: similar results, sensitive to initial guess

Point estimates

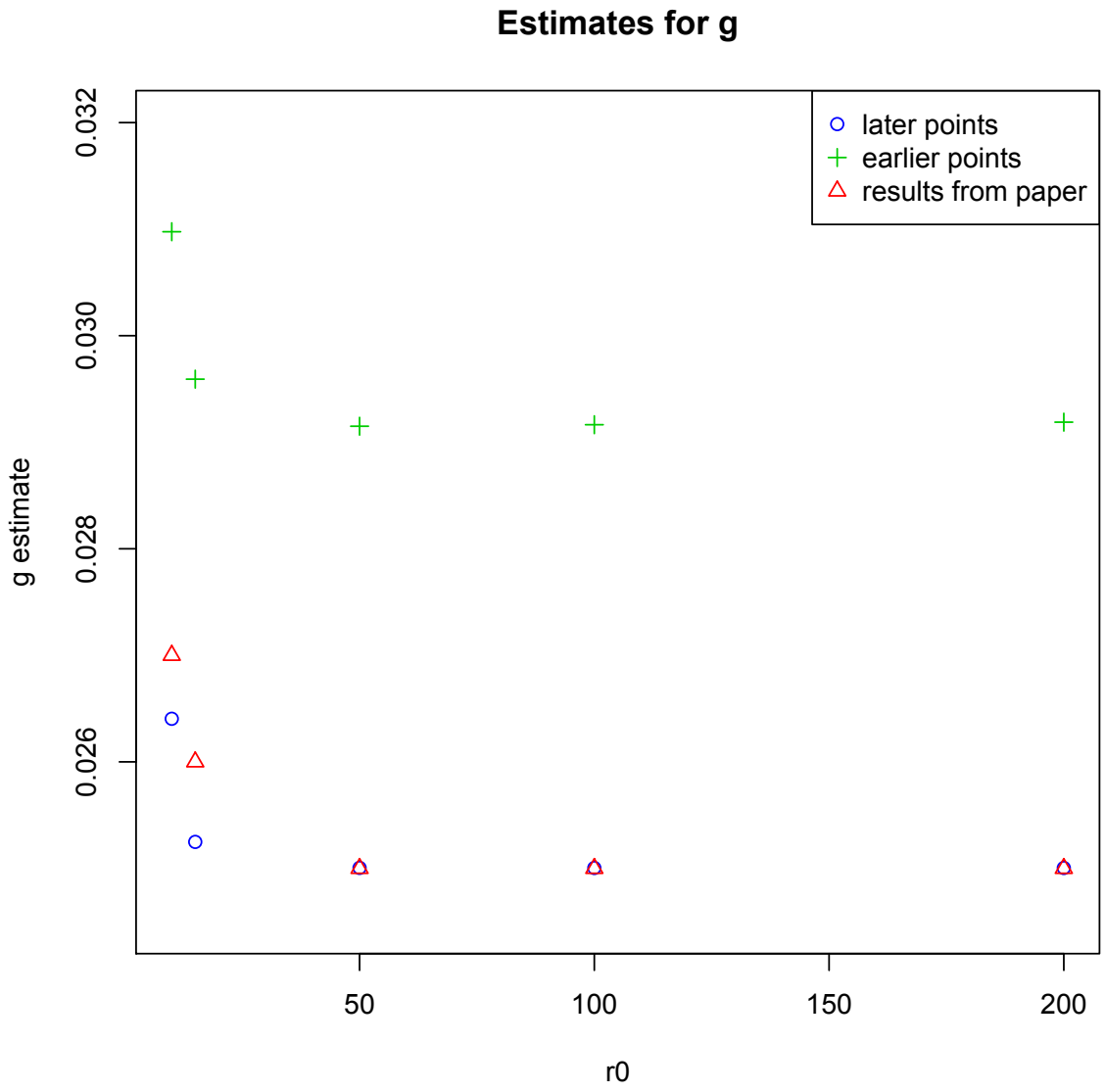
Given in terms of $p = \frac{\lambda}{\lambda+\nu}$ and $g = \lambda - \nu$, over range of r_0

- Interpretation: p is probability that a given decision in reserve is self-renewal, g is the intensity of the reserve
- Similar to results from paper, but not identical
- Could be due to differing dataset, or choice of observations

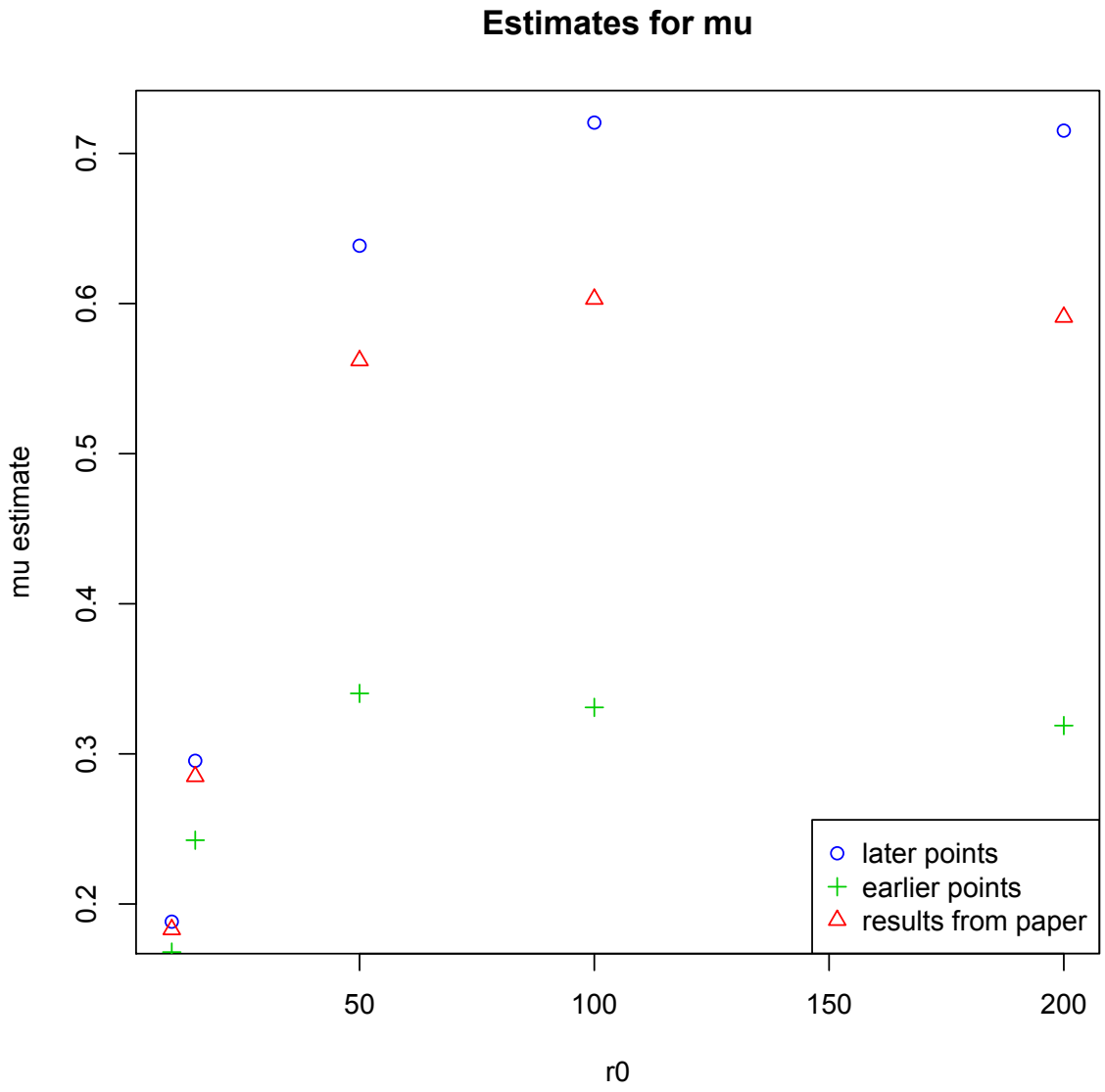
Point estimates: p



Point estimates: g



Point estimates: μ



What's next

- Solve using data from all time points using non-linear least squares
- Understand and compute standard errors
- Simulation and validation starting with point estimates
- Investigate transition probability calculations: re-derive Kolmogorov equation for pseudo-generating functions