Modelling and optimisation of group dose-response challenge experiments

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Experimental Design

- An experiment is a scientific procedure undertaken to make a discovery, test a hypothesis or demonstrate a known fact
  - Procedure
  - Subjects
  - Time(s) to observe experiment
Optimal Experimental Design

Control Variables → Experiment → Statistical Criterion
Statistical Criterion

- Given the log-likelihood

\[ \ell = \log(L(\theta)) \]

The Fisher information is

\[ I_{i,j} = \mathbb{E} \left[ \left( \frac{\partial \ell}{\partial \theta_i} \right) \left( \frac{\partial \ell}{\partial \theta_j} \right) \right] \]

- Related to the variance of parameter estimates
Optimality Criterion

Many different optimality criteria that look at minimising the variance of the parameter estimates.

**E-Optimality:**  Maximise the smallest eigenvalue of $\mathcal{I}$
Minimise variance of parameter estimate with largest variance

**A-Optimality:**  Maximise trace of $\mathcal{I}$
Minimise average variance of parameter estimates

**D-Optimality:**  Maximise determinant of $\mathcal{I}$
Minimise the generalised variance of the parameter estimates
Frequentist Experimental Design

- Choose design that satisfies chosen criterion
- Locally optimal
- Require knowledge about the parameter in order to determine the optimal design
Frequentist Example

- Exponential lifetimes; $F(t) = 1 - \exp(-t\theta)$

\[
\mathcal{I}(\theta, t) = \frac{t^2 \exp(-t\theta)}{1 - \exp(-t\theta)}
\]

\[
\frac{\partial \mathcal{I}}{\partial t} = \frac{t \exp(-t\theta)(2 - 2 \exp(-t\theta) - t\theta)}{(1 - \exp(-t\theta))^2}
\]

- Maximised when $t \approx 1.5936/\theta$
Bayesian Optimal Experimental Design

- Allows incorporation of prior knowledge into design
- Choose a utility function that we wish to maximise
- Expected Kullback-Leibler divergence

\[ U(d) = \int \int \log \left( \frac{p(\theta | y, d)}{p(\theta)} \right) p(y, \theta | d) dy d\theta \]

- Maximise our gain in information
Optimal Experimental Design for Markov Chains

- Why Markov Chains?
- Open field of research
  - Becker and Kersting [1983]
  - Cook et al. [2008]
  - Pagendam and Pollett [2010]
  - Pagendam and Ross [2013]
  - Pagendam and Pollett [2013]
Dose-response challenge experiments

- Dose 1 → Chicken 1 → Not Infected
- Dose 2 → Chicken 2 → Not Infected
- Dose 3 → Chicken 3 → Infected
Dose-response relationship

![Graph showing the dose-response relationship between log10 dose and proportion of colonized hosts. The graph is a smooth curve, indicating a positive correlation.](image)

- **Y-axis:** Proportion of Colonized Hosts
- **X-axis:** log10 Dose

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References

- Dose-response relationship
- ANZAPW 2013
Dose-response relationship

![Graph showing a dose-response curve with ID_{50} and slope labeled.]
Group dose-response experiment with transmission

- **Dose 1**
  - Chicken 1
  - Not Infected

- **Dose 2**
  - Chicken 2
  - Infected

- **Dose 3**
  - Chicken 3
  - Infected
Dose-response relationship with transmission

![Graph showing the dose-response relationship with transmission. The x-axis represents the log10 dose, and the y-axis represents the proportion of colonized hosts. The graph includes two curves, one for the proportion of colonized hosts increasing with dose.](image-url)
Dose-response relationship with transmission

Proportion of Colonized Hosts

log_{10} Dose

ID_{50}
Modelling dose-response challenge experiments

- Conlan et al. [2011] first to account for transmission
- Two-stage process; dose-response and transmission
- Need to take into account latency period of dose-response
- Create SEIR model (Susceptible, Exposed, Infected, Removed)
Optimal Design for some epidemic models

- Pagendam [2010] and Pagendam and Pollett [2013] looked at optimal design for experimental epidemics
- Locally optimal design of the SIS epidemic
- Likelihood evaluation computationally expensive
Recall: SIS epidemic

- State space is number of infected individuals \((0, \ldots, N)\)
- Transition rates are
  - \(q_{i,i+1} = \frac{\beta i (N-i)}{N}\)
  - \(q_{i,i-1} = \mu i\)
- Estimate parameters \((\rho, \alpha)\), where \(\rho = \frac{\mu}{\beta}\) and \(\alpha = \beta - \mu\)
- Nice physical interpretation
An SIS epidemic, $\alpha = 3$, $\rho = 0.25$
An SIS epidemic, $\alpha = 3, \rho = 0.25$
An SIS epidemic, $\alpha = 3, \rho = 0.25$
An SIS epidemic, $\alpha = 3$, $\rho = 0.25$
Overestimating $\alpha$

Figure: Densities of MLE’s for $(\rho, \alpha)$. True values are $(0.25, 3)$. 
Does Bayes have a problem?

- Kullback-Leibler divergence looks to maximise the difference between the prior and posterior.
- What if our posterior distribution for the ‘bad’ design is “further away” than the posterior for the ‘good’ design?
Example

![Graph showing density vs. α with a peak at some value of α.

'Good' likelihood curve highlighted in blue.]

References
Example

![Graph showing two peaks labeled 'Bad' likelihood with density on the y-axis and \( \alpha \) on the x-axis.]

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Example
Example

Figure: Example prior and two likelihood functions
Figure: Discretised example prior and likelihood functions
Figure: Discretised example prior and posterior distributions
Good KLD = 0.007
Bad KLD = 0.098

Figure: Discretised example prior and posterior distributions
Warning!

- Kullback-Leibler divergence is not a “black box”!
- Check:
  - Posterior
  - Prior
  - Design
- Care needs to be taken when using KLD for Bayesian Optimal design
Research Aims

- Investigate Kullback-Leibler divergence further
- Intractable likelihood for SEIR model
- Compare results of different design approaches for the SIS epidemic
- Move on to developing the SEIR model and applying these methods to that model
Thank you

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  - Prof. Nigel Bean,
  - Dr Joshua Ross, and
  - Dr Jonathan Tuke

- Daniel Pagendam for correspondence.

- Everyone for listening!
References


Gaussian Diffusion Approximation of the Likelihood

- Matrix exponentials computationally inefficient, especially as population size grows
- Kurtz [1970]
- The expected value of the SIS process over time, follows the deterministic trajectory.
- $\Sigma$ is the covariance matrix, $y$ is the observed number of infected at the observation times, and $m$ is the corresponding mean number of infected at those times
- Very computationally efficient

$$ L(\theta; y \mid y_0) = $$

$$(2\pi)^{-n/2} |N\Sigma|^{-1/2} \exp \left( -\frac{1}{2} (y - Nm) \frac{\Sigma^{-1}}{N} (y - Nm)^T \right) $$
Likelihood for ‘bad’ design
Likelihood for ‘good’ design