Efficient Likelihood Approximation via Gaussian Processes

With an Application to a *P. Vivax* Malaria Model

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Introduction and Motivation

- 600,000 deaths/year, 75% children under 5
- Two main species *P. vivax* and *P. falciparum*
- *P. falciparum* main cause of death, but *P. vivax* historically underestimated.
- Proportion of *P. vivax* cases increased over last 50 years.

P. vivax has Dormant Stage

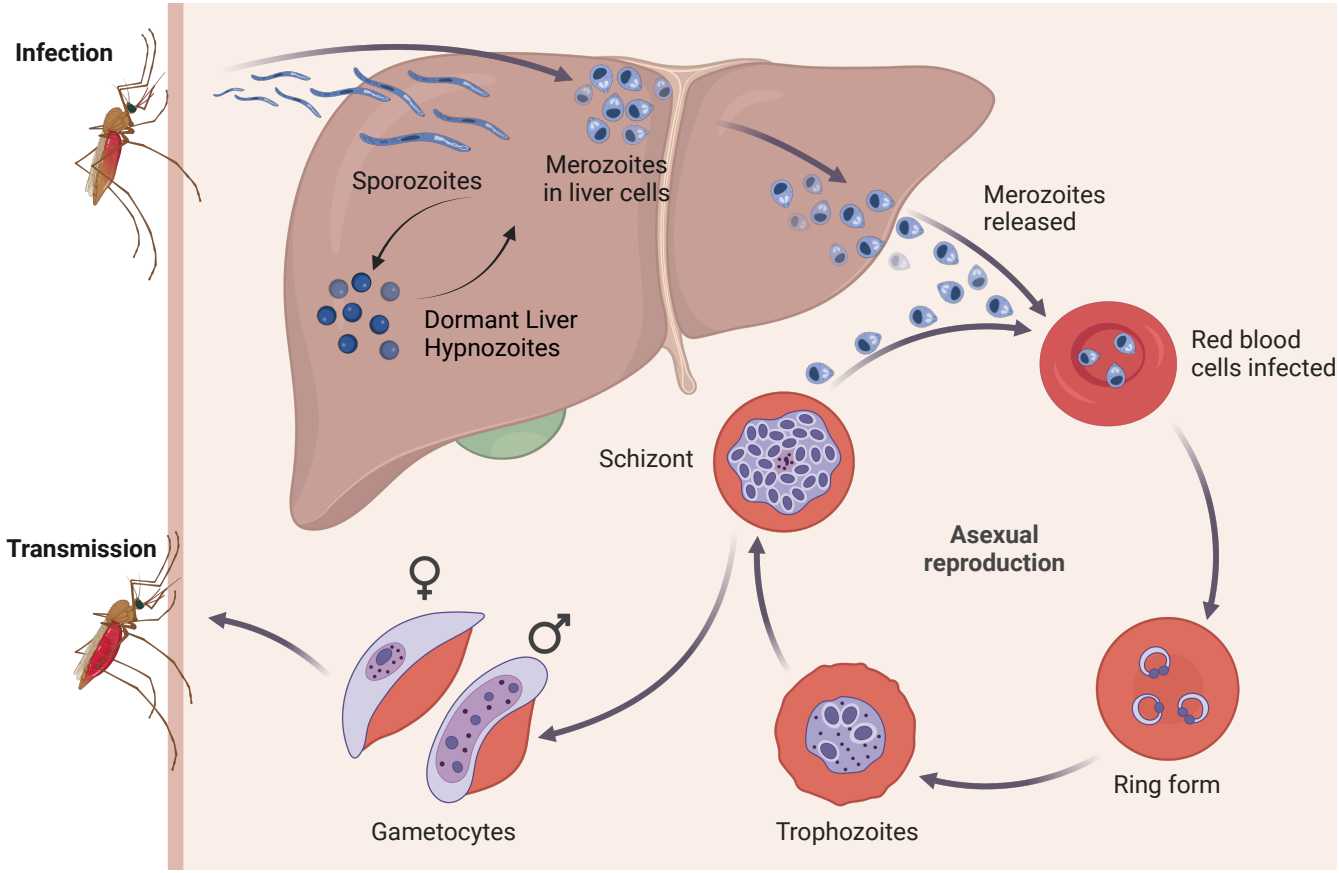

Figure: *P. vivax* lifecycle. Created with BioRender.com

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Vivax Model - Champagne et. al

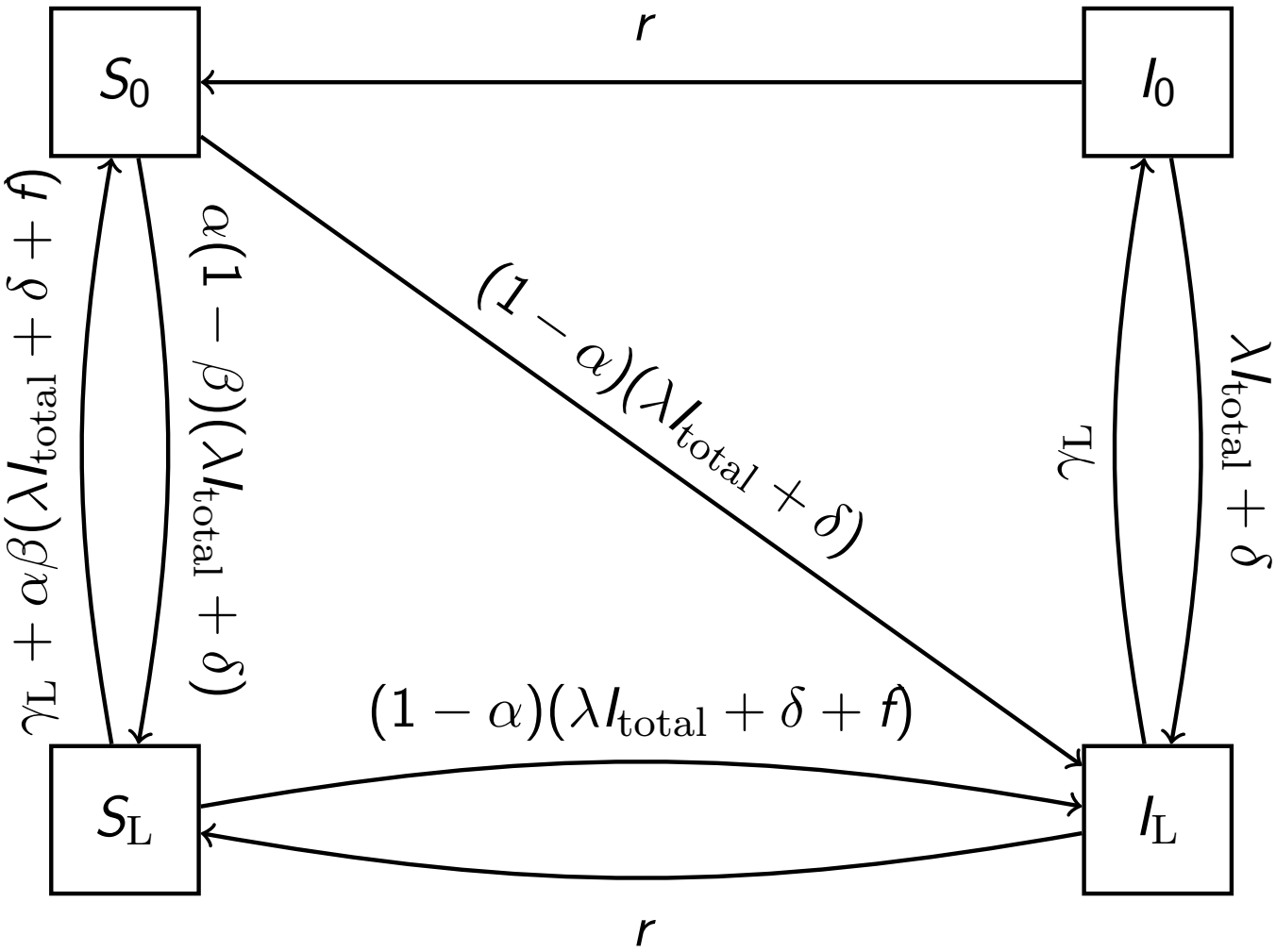

Figure: Champagne et al. 2022 *P. vivax* model

Champagne Model Parameters

- α : proportion of those infected who clear blood stage infections through treatment
- β : proportion of those cleared of blood stage infection who are also cleared of liver stage parasites (radical cure)
- λ : rate of infection
- γ_L : rate of liver stage disease clearance
- f : rate of relapse
- r : rate of blood stage clearance
- $\delta = 0$ importation rate (fixed)

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The Problem

- How to calibrate model parameters?

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- Simulations take long time (and models get a lot more complicated)

Notation

- $\boldsymbol{\theta}$ vector of parameters - e.g. $[\alpha, \beta, \gamma_L, \lambda, f, r]^T$
- $\mathbf{Y}_{\text{obs}}$: a (summary) vector of observed data e.g. (weekly) incidence, prevalence, (monthly) hospitalisations

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- $\boldsymbol{\theta}$ vector of parameters - e.g. $[\alpha, \beta, \gamma_L, \lambda, f, r]^T$
- $\mathbf{Y}_{\text{obs}}$: a (summary) vector of observed data e.g. (weekly) incidence, prevalence, (monthly) hospitalisations
- $\mathbf{Y}_{\boldsymbol{\theta}}$: a random vector of model statistics for given $\boldsymbol{\theta}$.

In an ideal world...

- There would be an explicit form for the likelihood:

$$\mathcal{L}(\boldsymbol{\theta}) := \Pr(\mathbf{Y}_{\boldsymbol{\theta}} = \mathbf{Y}_{\text{obs}} | \boldsymbol{\theta})$$

- $\hat{\boldsymbol{\theta}} = \arg\max_{\boldsymbol{\theta}} \mathcal{L}(\boldsymbol{\theta})$
- $\Pr(\boldsymbol{\theta} | \mathbf{Y}_{\text{obs}}) \propto \mathcal{L}(\boldsymbol{\theta}) \Pr(\boldsymbol{\theta})$
- Off to the pub

Or not...

- Explicit likelihoods often don't exist/are intractible
  - Champagne model
  - Agent based models.

A Standard Bayesian Solution

- Approximate Bayesian Computation (ABC)
  1. Sample $\boldsymbol{\theta}_i$ from prior
  2. Run model and observe $\mathbf{Y}_{\boldsymbol{\theta}_i}$
  3. Accept or reject $\boldsymbol{\theta}_i$ run based on how well $\mathbf{Y}_{\boldsymbol{\theta}_i}$ 'matches' $\mathbf{Y}_{\text{obs}}$.

What is 'matches'?

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   - Good luck...
2. Rescale $\mathbf{Y}$s, and use discrepency function $D : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$ e.g. p-norm

$$D(\mathbf{Y}_{\boldsymbol{\theta}_i}, \mathbf{Y}_{\text{obs}}) := \left(\sum_{j=1}^{d} |\{\mathbf{Y}_{\boldsymbol{\theta}_i}\}_j - \{\mathbf{Y}_{\text{obs}}\}_j|^p \right)^{1/p}$$

Discrepency Function

$\mathcal{D}(\boldsymbol{\theta}) := D(\mathbf{Y}_{\boldsymbol{\theta}}, \mathbf{Y}_{\text{obs}})$ how 'close' our model is to the observed data using parameters $\boldsymbol{\theta}$

ABC

1. Sample $\boldsymbol{\theta}_i$ from prior
2. Run model
3. Accept $\boldsymbol{\theta}_i$ if $\mathcal{D}(\boldsymbol{\theta}_i) < \varepsilon$.

Overall Idea of my Research

- ABC fixes one problem but leaves another:
  - Don't need $\mathcal{L}(\boldsymbol{\theta})$.
  - Evaluating $\mathcal{D}(\boldsymbol{\theta})$ takes as long as a model run.

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- ABC fixes one problem but leaves another:
  - Don't need $\mathcal{L}(\boldsymbol{\theta})$.
  - Evaluating $\mathcal{D}(\boldsymbol{\theta})$ takes as long as a model run.
- $\mathcal{D}(\boldsymbol{\theta}), \mathcal{D}(\boldsymbol{\theta}')$ will be highly correlated when $\boldsymbol{\theta}$ is near $\boldsymbol{\theta}'$.
  - Gaussian Processes

Gaussian Process Setup

Formally we can assume that

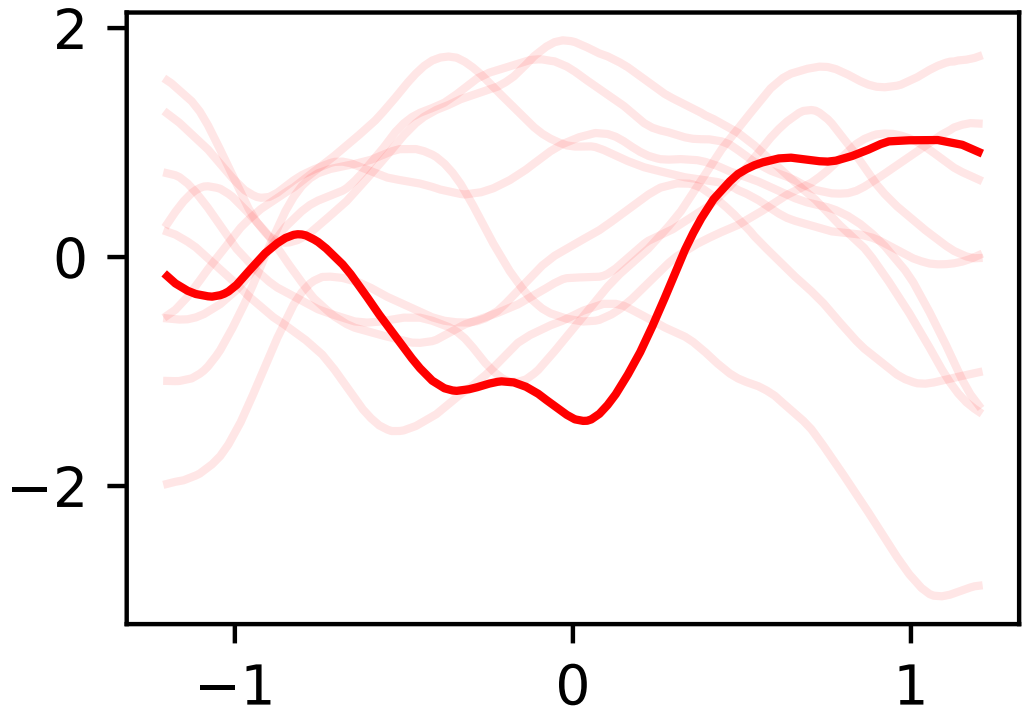
$$\mathrm{Cov}(\mathcal{D}(\boldsymbol{\theta}_i), \mathcal{D}(\boldsymbol{\theta}_j)) = k(\boldsymbol{\theta}_i, \boldsymbol{\theta}_j)$$

for some covariance kernel k that decays to 0 as $\boldsymbol{\theta}_i$ is further away than $\boldsymbol{\theta}_j$.

Gaussian Processes on $\mathbb{R}^d$

Definition (Gaussian Process)

A collection of random variables $\{f(\mathbf{x})\}_{\mathbf{x}\in\mathbb{R}^d}$ is a Gaussian process if all finite dimensional distributions are multivariate normal distributed.



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Gaussian Process Continuity

- Induce continuity by forcing $k(\mathbf{x}, \mathbf{x}') \to \mathrm{Var}(f(\mathbf{x}))$ (hence $\mathrm{Cor}(f(\mathbf{x}), f(\mathbf{x}')) \to 1$) as $\mathbf{x} \to \mathbf{x}'$.

Common Covariance Kernels

- Choice of kernel determines smoothness
- Matérn Kernel with hyperparameter ν : $\lfloor \nu \rfloor$ times mean square differentiable.
- $\nu \to \infty$: infinitely mean square differentiable squared exponential covariance kernel (strong assumption)

$$k(x, x') = \sigma_k^2 \exp(-\frac{||x - x'||^2}{2\ell^2})$$

k Determines Class of Functions

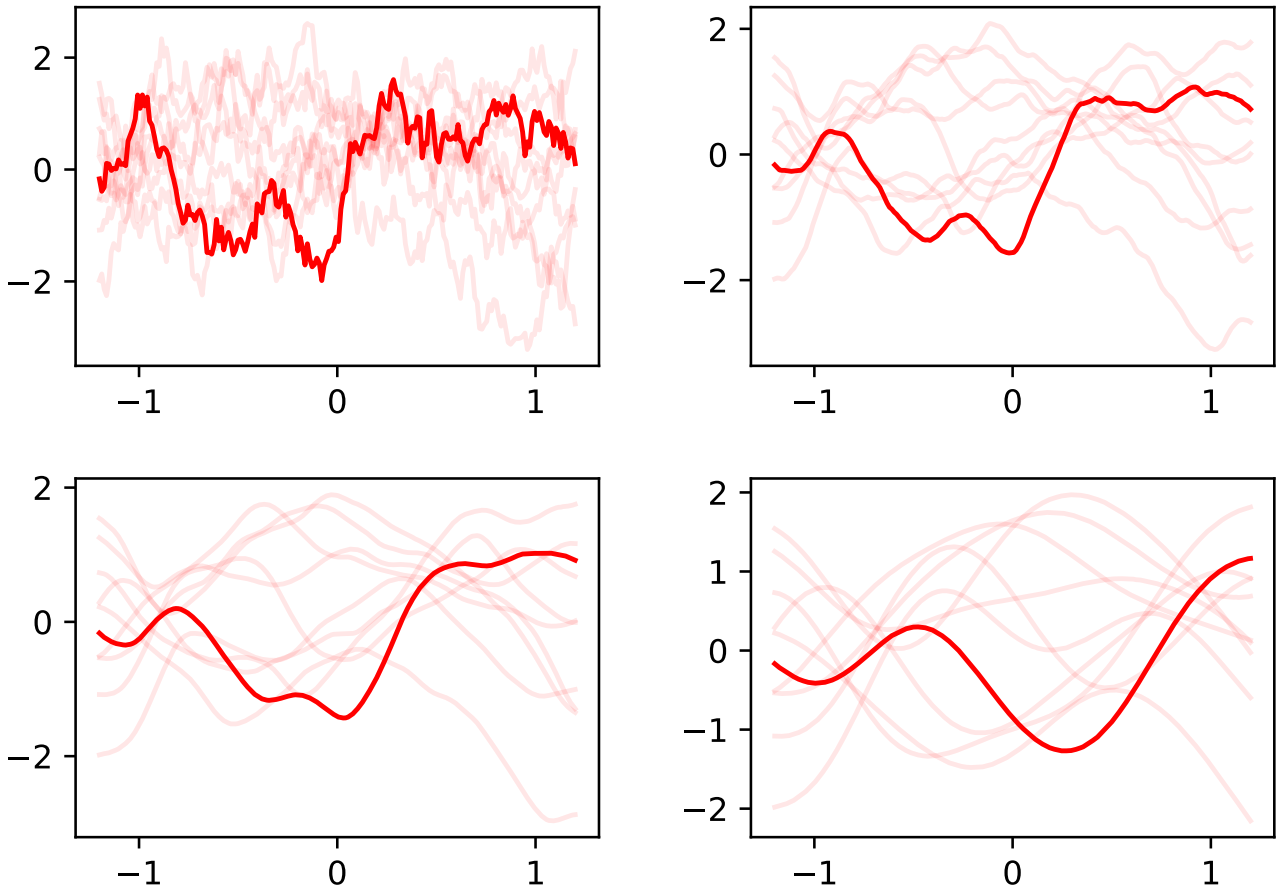

Figure: Matérn 1/2, 3/2, 5/2, and squared exponential kernels.

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Kernel Hyperparameters

- Matérn and squared exponential kernel can both be written in the form $k(\mathbf{x}, \mathbf{x}') = \sigma_k^2 \kappa(||\mathbf{x}, \mathbf{x}'||/\ell)$
- $1/\ell$ rate of covariance decay
- $\sigma_k^2 = \mathrm{Var}(f(\mathbf{x}))$

Discrepency Function Context

- Long term play: replace $\mathcal{D}(\boldsymbol{\theta})$ with a Gaussian process surrogate model approximation.

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- Long term play: replace $\mathcal{D}(\boldsymbol{\theta})$ with a Gaussian process surrogate model approximation.
- What if we have observations already?

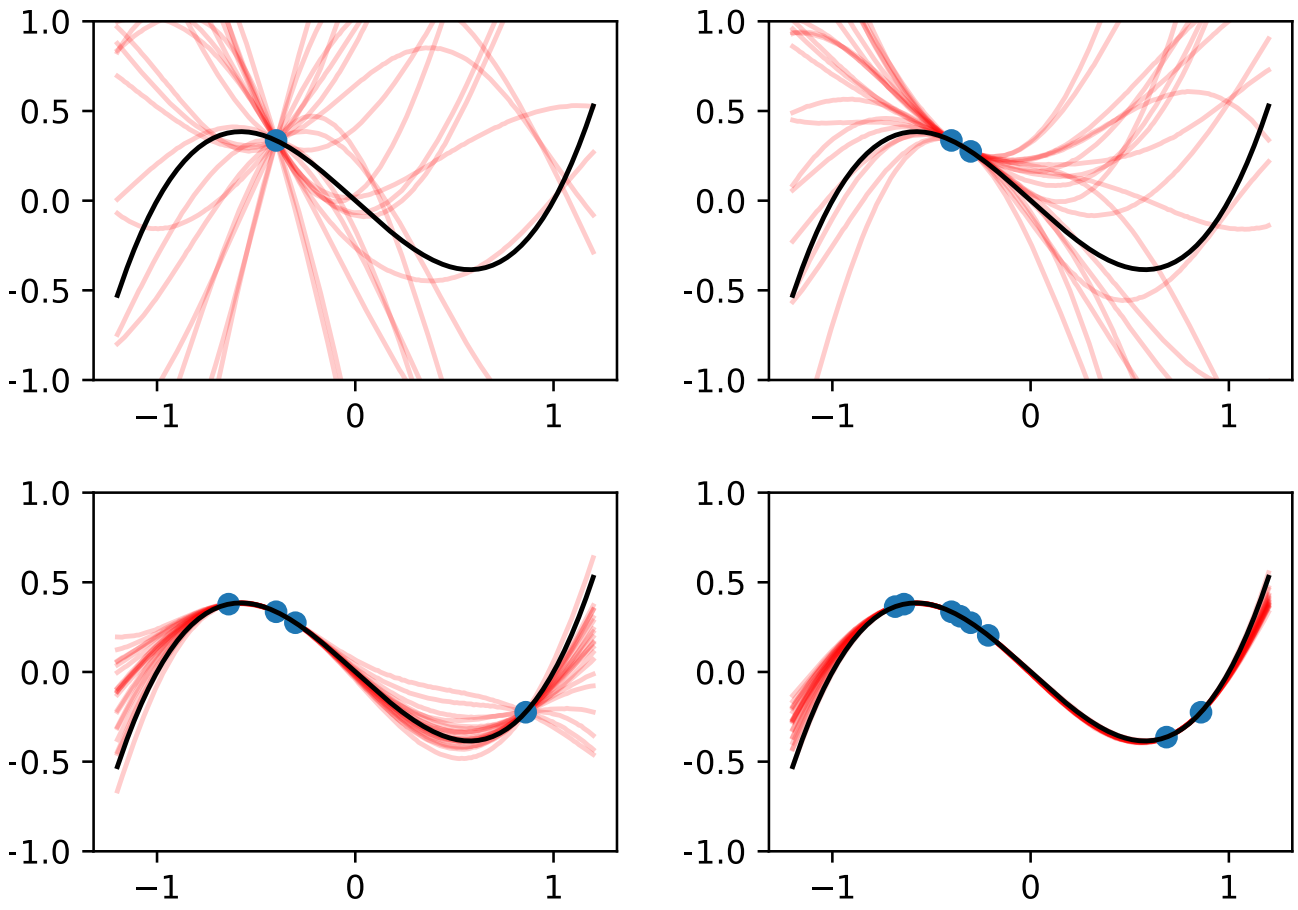
Gaussian Process Regression

$$\begin{bmatrix} f(\mathbf{x}) \\ f(\mathbf{x}_*) \end{bmatrix} \sim \text{MVN}\left(\begin{bmatrix} m(\mathbf{x}) \\ m(\mathbf{x}_*) \end{bmatrix}, \begin{bmatrix} K & K_* \\ K_*^T & K_{**} \end{bmatrix} \right)$$

implies

$$f(\mathbf{x})|f(\mathbf{x}_*) \sim \text{MVN}\left(m(\mathbf{x}) + K_* K_{**}^{-1}(f(\mathbf{x}_*) - m(\mathbf{x}_*)),\ K - K_* K_{**}^{-1} K_*^T\right).$$

GP regression on $x(x-1)(x+1)$



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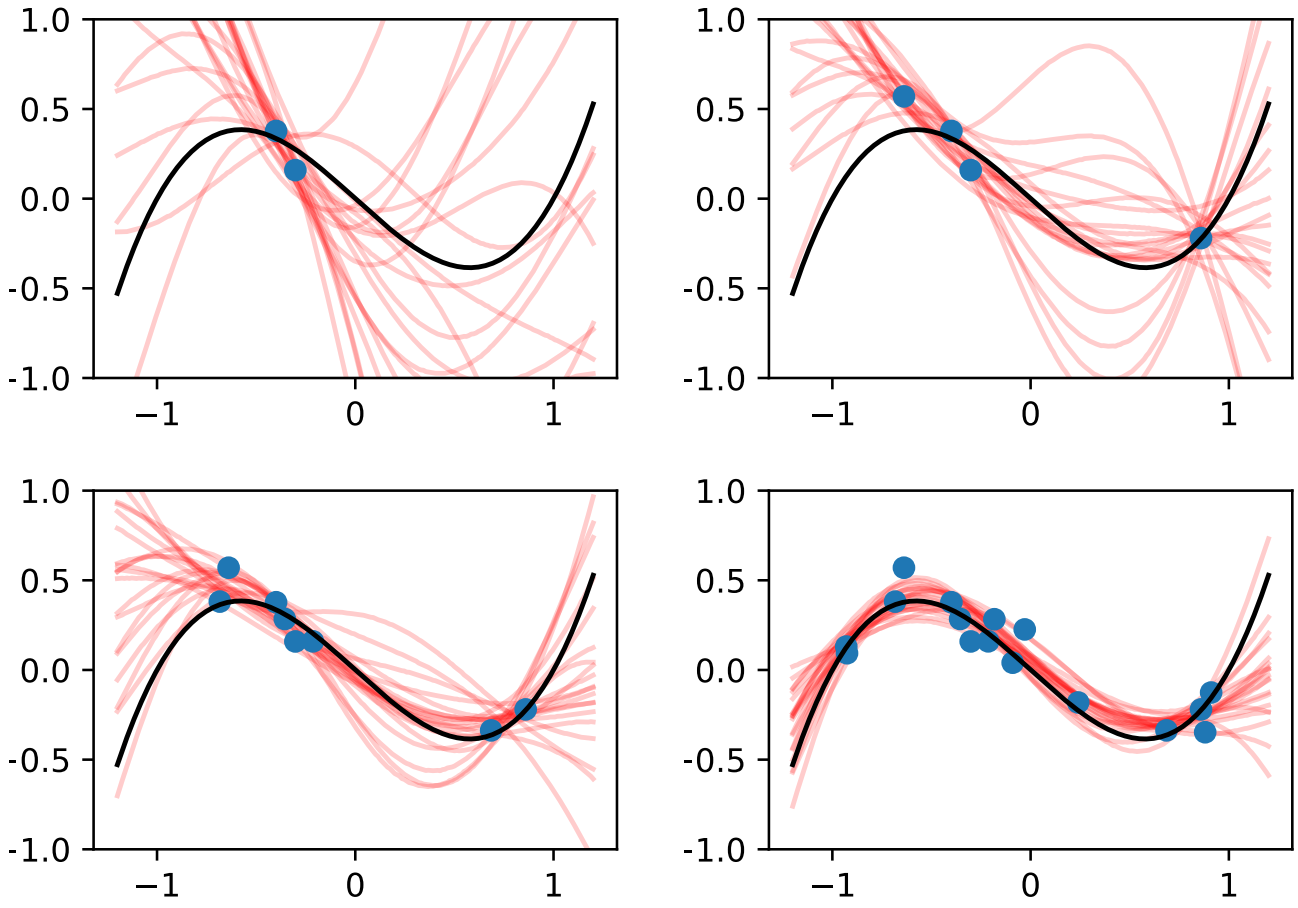
Normal observation noise

If observations actually $f(\mathbf{x}_i) + \varepsilon_i$, with $\varepsilon_i \sim N(0, \sigma_o^2)$ i.i.d., then

$$\begin{bmatrix} f(\mathbf{x}_1) + \varepsilon_1 \\ \vdots \\ f(\mathbf{x}_n) + \varepsilon_n \end{bmatrix} \sim \text{MVN}\left(\begin{bmatrix} m(\mathbf{x}_1) \\ \vdots \\ m(\mathbf{x}_n) \end{bmatrix}, \mathbf{K} + \sigma_o^2 \mathbf{I}_n \right)$$

GP regression on $x(x-1)(x+1)+\varepsilon,\ \varepsilon \sim N(0, \sigma_o^2)$



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Key Idea

- If $\mathbb{E}[\mathcal{D}(\boldsymbol{\theta})]$ can be well approximated by a Gaussian process and ...

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- If $\mathbb{E}[\mathcal{D}(\boldsymbol{\theta})]$ can be well approximated by a Gaussian process and ...
- $\mathcal{D}(\boldsymbol{\theta})$ approximately distributed $N(\mathbb{E}[\mathcal{D}(\boldsymbol{\theta})], \sigma_o^2)$ then...
- Approximate $\mathcal{D}(\boldsymbol{\theta})$ with $\mathcal{D}_{\mathcal{GP}}(\boldsymbol{\theta})$, a Gaussian process with observation noise.

ABC

1. Sample $\boldsymbol{\theta}_i$ from prior
2. Run model
3. Accept $\boldsymbol{\theta}_i$ if $\mathcal{D}(\boldsymbol{\theta}_i) < \varepsilon$.

Approximate ABC...??

1. Sample $\boldsymbol{\theta}_i$ from prior
2. ~~Run model~~ Simulate $\mathcal{D}_{\mathcal{GP}}(\boldsymbol{\theta}_i) \overset{d}{\approx} \mathcal{D}(\boldsymbol{\theta}_i)$
3. Accept $\boldsymbol{\theta}_i$ if $\mathcal{D}_{\mathcal{GP}}(\boldsymbol{\theta}_i) < \varepsilon$.

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Synthetic Likelihood

Pr drawing and accepting $\boldsymbol{\theta}$ using 'approximate' ABC is

$$\Pr(\mathcal{D}_{\mathcal{GP}}(\boldsymbol{\theta}) < \varepsilon) \Pr(\boldsymbol{\theta})$$

and hence

$$\hat{L}(\boldsymbol{\theta}) := \Pr(\mathcal{D}_{\mathcal{GP}}(\boldsymbol{\theta}) < \varepsilon) \approx c\mathcal{L}(\boldsymbol{\theta})$$

for some c.

Log Gaussian Process

- Alternatively we can model $\ln \mathcal{D}(\boldsymbol{\theta})$ as a Gaussian process $d_{\mathcal{GP}}(\boldsymbol{\theta})$.

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Log Gaussian Process

- Alternatively we can model $\ln \mathcal{D}(\boldsymbol{\theta})$ as a Gaussian process $d_{\mathcal{GP}}(\boldsymbol{\theta})$.
- Key assumptions becomes:
  - $\mathcal{D}(\boldsymbol{\theta})$ approximately distributed $LN(\cdot, \sigma_o^2)$.
- $$\hat{L}(\boldsymbol{\theta}) := \Pr(d_{\mathcal{GP}}(\boldsymbol{\theta}_i) < \ln \varepsilon) \approx \Pr(\mathcal{D}(\boldsymbol{\theta}_i) < \varepsilon)$$

Where to sample $\mathcal{D}(\boldsymbol{\theta})$

- To generate a reliable $\mathcal{D}_{\mathcal{GP}}$, we need to sample widely
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- Therefore sample where:

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- Generating $\mathcal{D}(\boldsymbol{\theta})$ still costly...
- Therefore sample where:
  - $\mathbb{E}[\mathcal{D}(\boldsymbol{\theta})]$ small,
  - $\mathcal{D}(\boldsymbol{\theta})$ highly unknown.

Bayesian Acquisition Functions

- $\mu(\boldsymbol{\theta}) := \mathbb{E}(D_{\mathcal{GP}}(\boldsymbol{\theta}))$ and $\mathrm{v}(\boldsymbol{\theta}) := \mathrm{Var}(D_{\mathcal{GP}}(\boldsymbol{\theta}))$
- Bayesian acquisition functions $A(\boldsymbol{\theta})$, quantify how 'desirable' it is to sample $\mathcal{D}(\boldsymbol{\theta})$ at $\boldsymbol{\theta}$.

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- Bayesian acquisition functions $A(\boldsymbol{\theta})$, quantify how 'desirable' it is to sample $\mathcal{D}(\boldsymbol{\theta})$ at $\boldsymbol{\theta}$.
- Gutmann and Cor 2016 minimise lower confidence bound

$$A_{\mathrm{LCB}}(\boldsymbol{\theta}) := \mu(\boldsymbol{\theta}) - \eta_t \sqrt{\mathrm{v}(\boldsymbol{\theta})},$$

the lower value of a confidence interval (determined by η_t).

Procedure

1. **Initialisation**: Sample $\mathcal{D}(\boldsymbol{\theta})$ at random $\boldsymbol{\theta}$, and train $\mathcal{D}_{\mathcal{GP}}$ on these points.

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3. Repeat 2.

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3. Repeat 2.
4. Use $\mathcal{D}_{\mathcal{GP}}$ to find $\hat{L}(\boldsymbol{\theta})$.
5. Use $\hat{L}(\boldsymbol{\theta})$ to calibrate parameters

Vivax Model - Champagne et. al

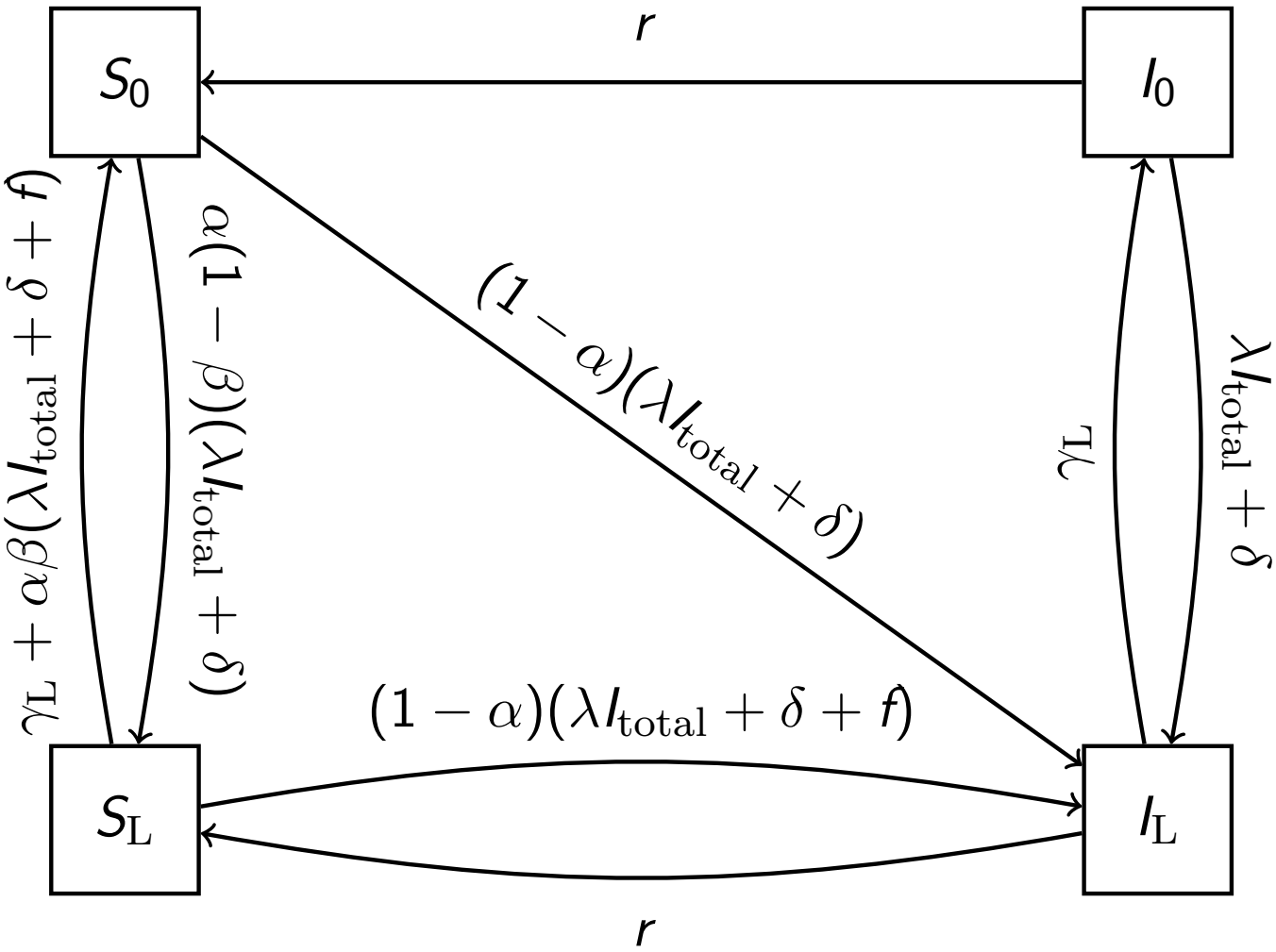

Figure: Champagne et al. 2022 *P. vivax* model

Champagne Model Parameters

- α : proportion of those infected but cleared of blood stage infections (through treatment)
- β : a further proportion that are also cleared of liver stage parasites, given that they were also cleared of blood stage infection (radical cure)
- λ : the rate of infection
- γ_L : rate of clearance of liver stage disease
- f : rate of relapse
- r : rate of blood stage clearance

Model Simulation

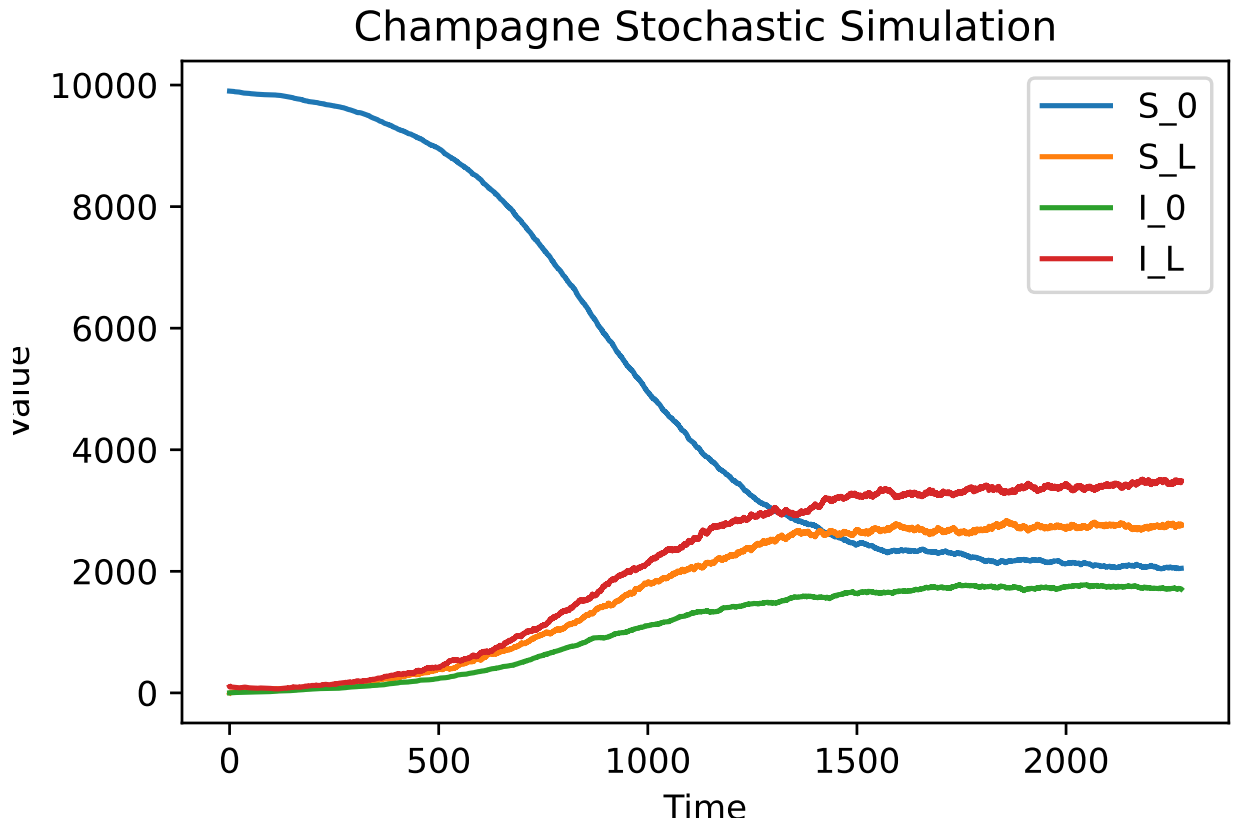

Figure: Exact stochastic simulation using parameters reported in Champagne et al. 2022. Population 10,000, initial infections 100.

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'Observed' Data

- $\mathbf{Y}_{\text{obs}} := \{\iota_{\text{obs}}, \pi_{\text{obs}}, i_{\text{obs}}, p_{obs}\}$
  - ι_{obs} : weekly incidence around steady state equilibrium
  - π_{obs} : prevalence around steady state equilibrium
  - i_{obs} : incidence in the first month of the epidemic
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  - ι_{obs} : weekly incidence around steady state equilibrium
  - π_{obs} : prevalence around steady state equilibrium
  - i_{obs} : incidence in the first month of the epidemic
  - p_{obs} : prevalence after one month of simulation
- $\mathcal{D}(\alpha, \beta, \gamma_L, \lambda, f, r)$ is the L_2 norm of the relative differences

$$\sqrt{\left(\frac{\iota - \iota_{\text{obs}}}{\iota_{\text{obs}}}\right)^2 + \left(\frac{\pi - \pi_{\text{obs}}}{\pi_{\text{obs}}}\right)^2 + \left(\frac{i - i_{\text{obs}}}{i_{\text{obs}}}\right)^2 + \left(\frac{p - p_{\text{obs}}}{p_{\text{obs}}}\right)^2}$$

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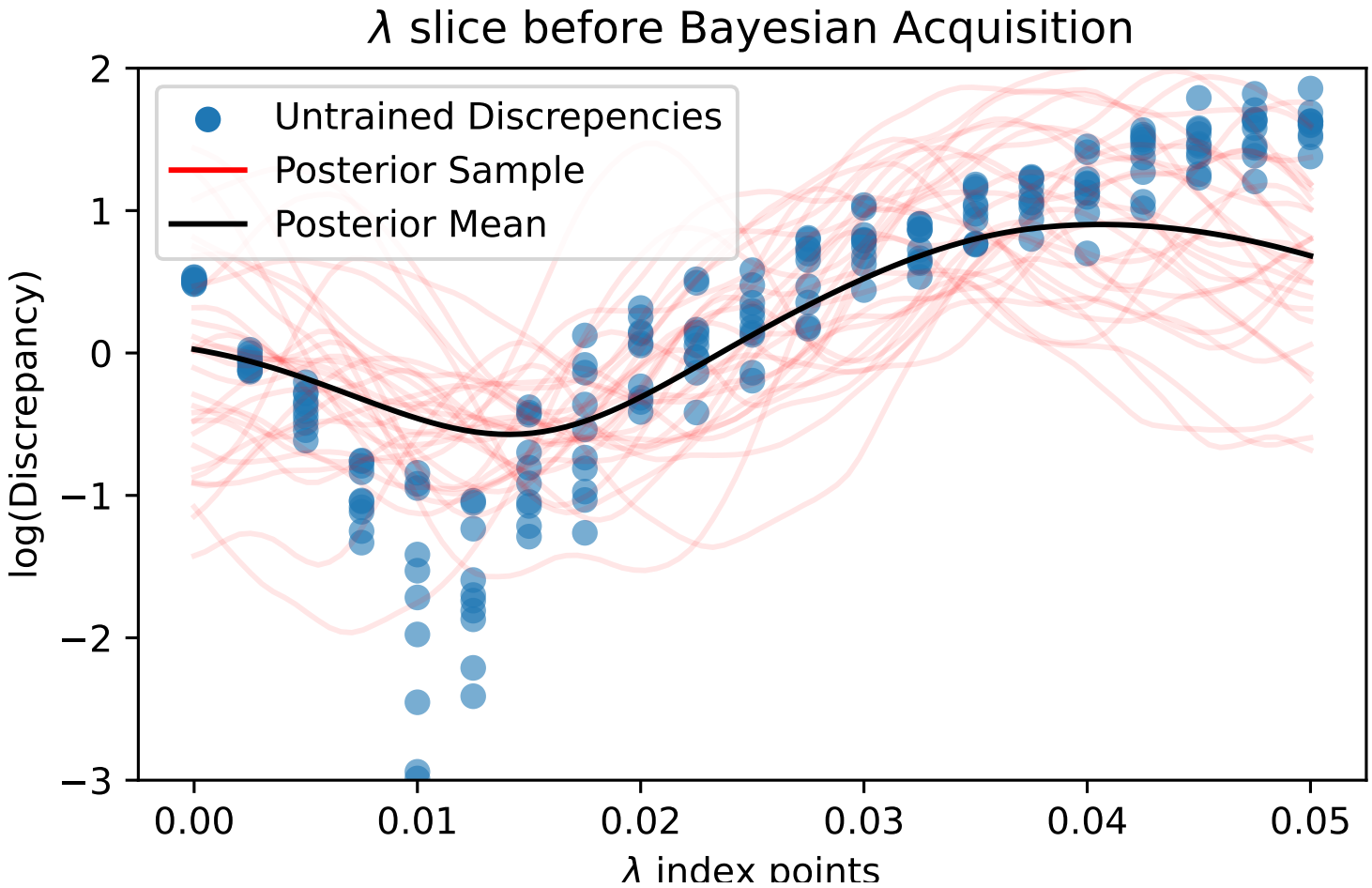
GP choices

- $\mathcal{GP}$ choices
  - Modelled $\ln \mathcal{D}$ as a Gaussian process
  - Matern kernel with $\nu = 5/2$
  - $\ell, \sigma_k^2, \sigma_o^2$ selected by leave one out cross validation.

Estimating rate of infection $\lambda = 0.01$



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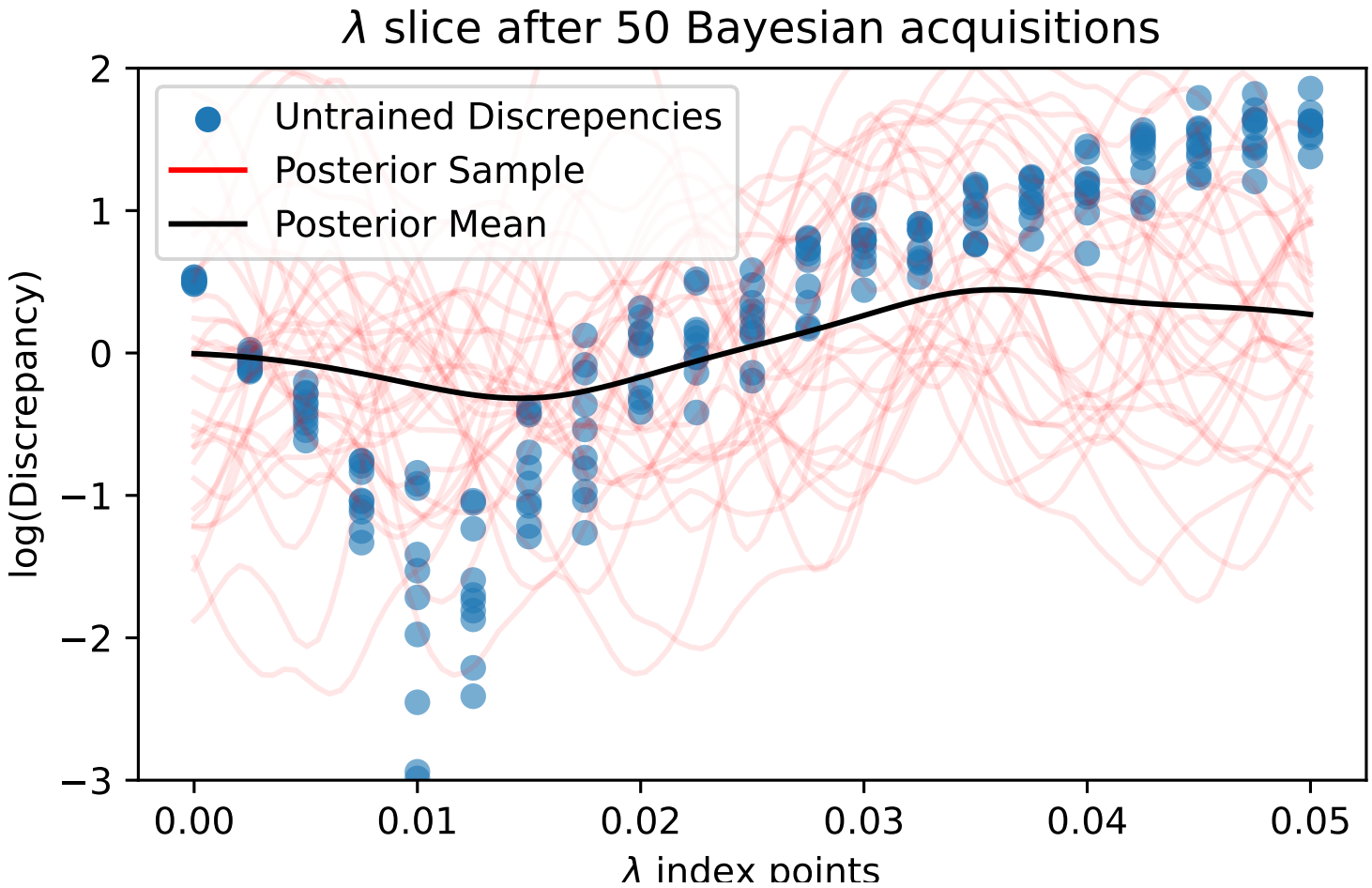

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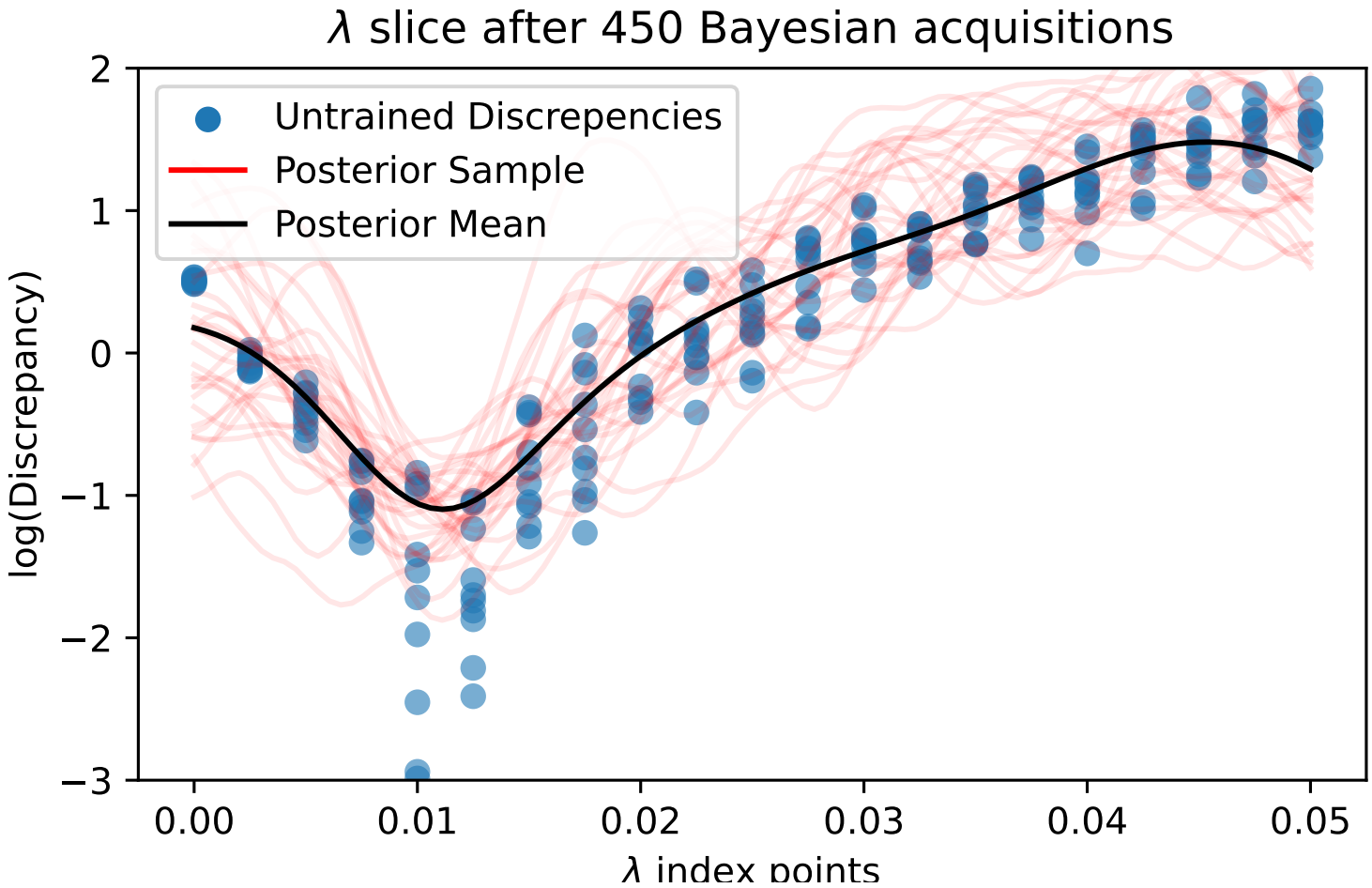

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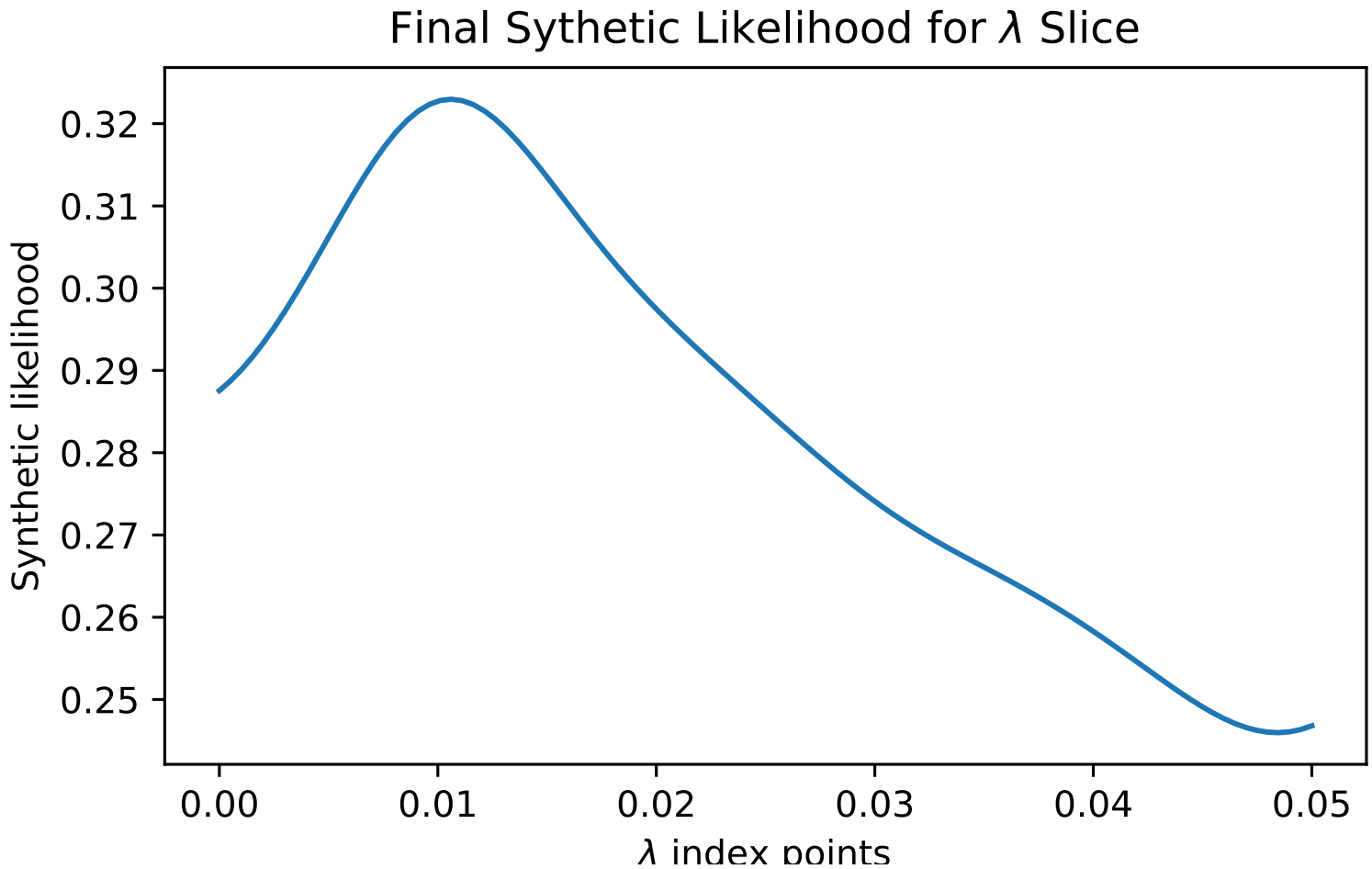
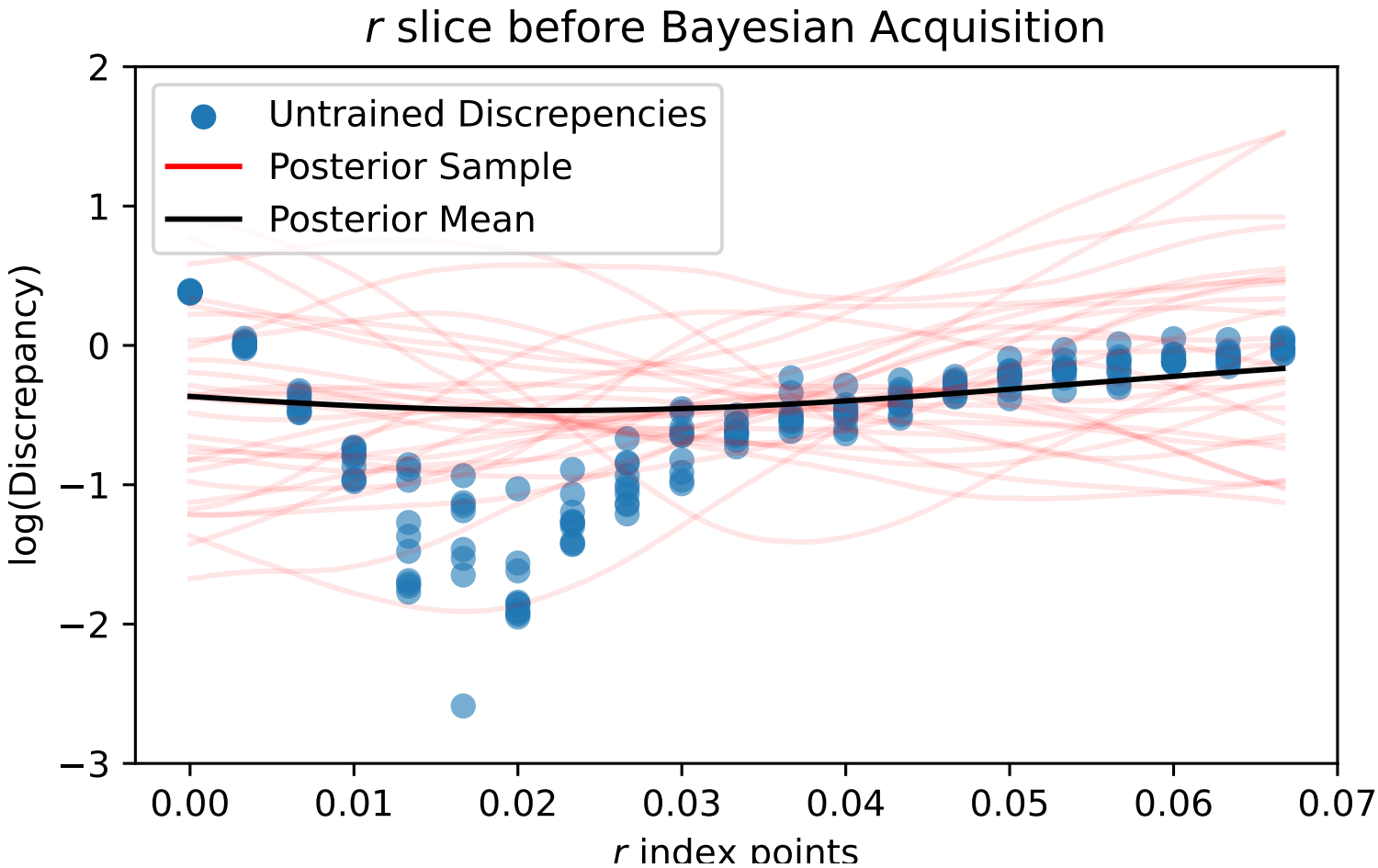


Estimating rate of blood stage clearance $r = 0.017$



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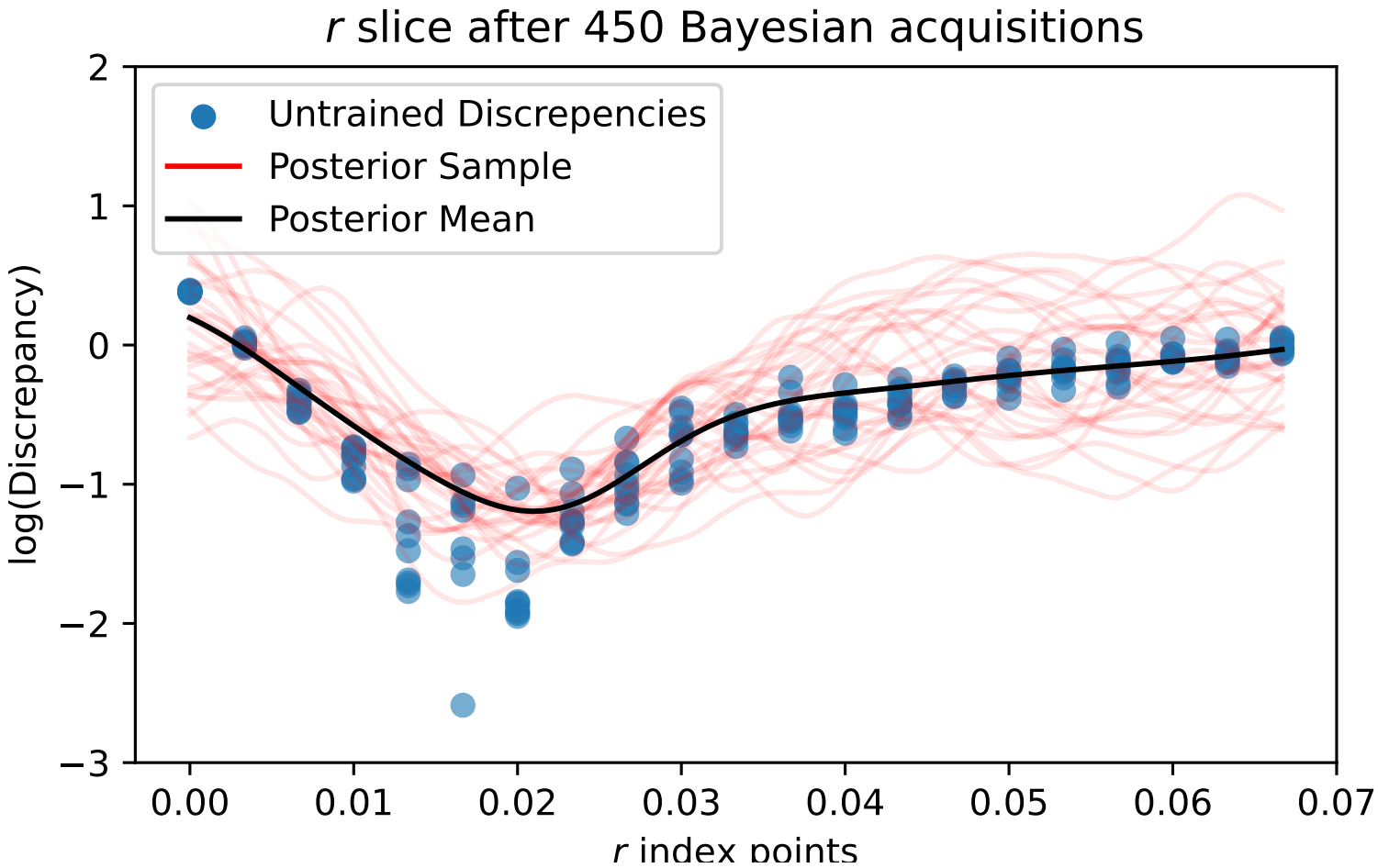

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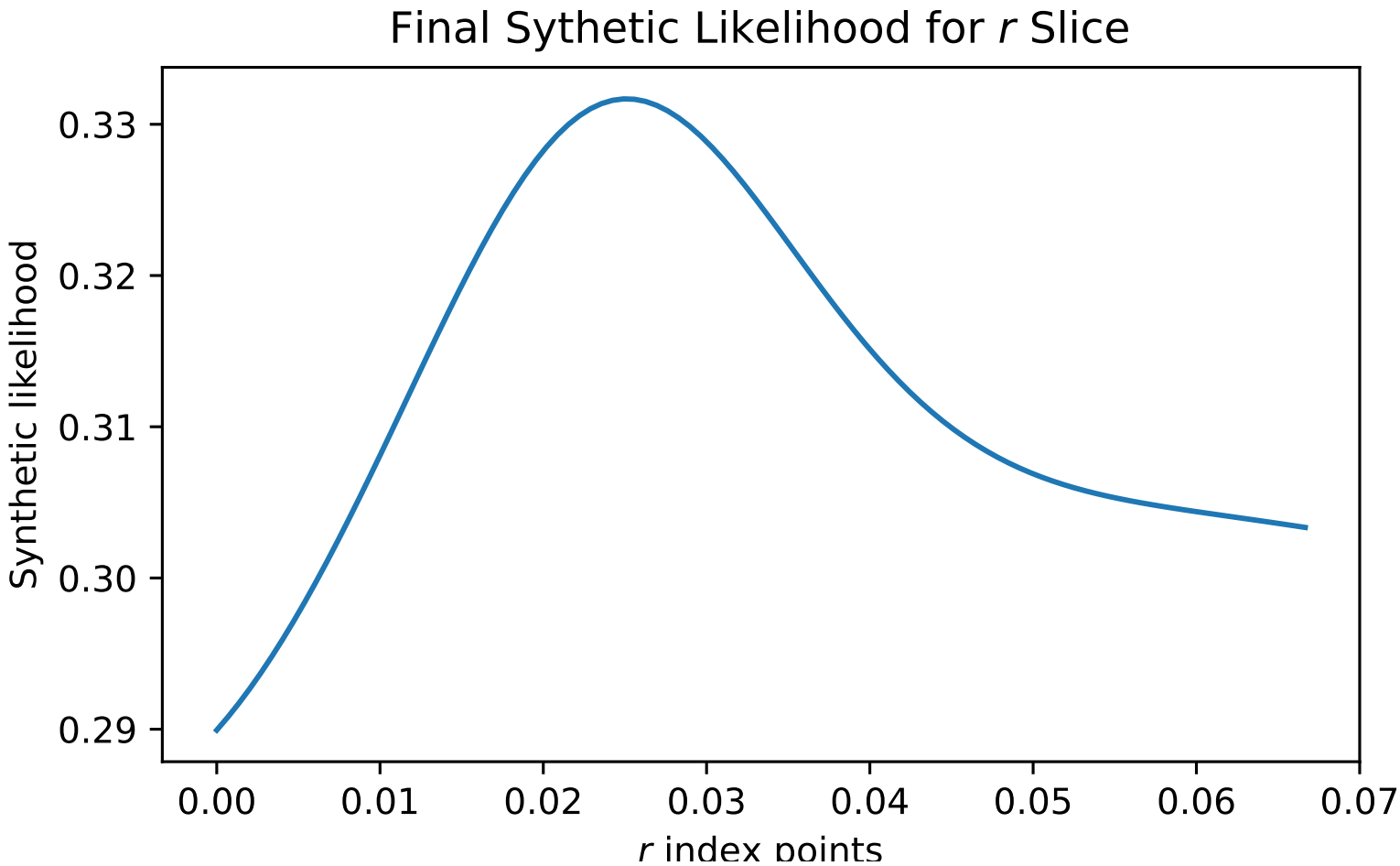

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Discussion

- Bifurcation points effect:
  1. observation variance,
  2. distribution of observations,
  3. behaviour of the discrepency mean.
- Possible extensions:

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- Possible extensions:
  1. model $s^2(\theta)$,
  2. choose a different distribution and moment match,
  3. use a Student's $t-$process.

Conclusion

- Calibrating model parameters is important for scenario testing etc
- Successfully calibrated model parameters
- Could be used with more complicated models, even your model...

Thanks to

- Eamon Conway
- Jennifer Flegg
- Ivo Mueller
- Mueller lab and unimelb MMB group

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