

# Master's Thesis

## An Empirical Bayes Method and its Application to a Systems Biology Model



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## Declaration

I hereby declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institute. Information derived from the published and unpublished work of others has been acknowledged in the text and a list of references is given.

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## 1 Introduction

This thesis will cover the development and application of an empirical Bayes method to the problem of parameter estimation in systems biology. The goal is to provide a general and practical solution to the Bayesian inverse problem in the case of high dimensional parameter spaces making use of present cohort-data.

Regarding it's application to systems biology or medicine a quantification of uncertainty of the results is of utmost importance to any practitioner facing decisions such as whether to apply a specific treatment or release a new drug.

Although the classical frequentist approach to statistics offers tools to answers to this in terms of confidence intervals and hypothesis tests, these techniques, aiming for point estimates, have a hard time dealing with ill-posed problems incorporating uncertainties and unidentifiabilities, often appearing in applications with large nonlinear models.

We will henceforth adopt the Bayesian view which, contrary to the point estimates in the frequentist approach, naturally confines the treatment of uncertainty by its description in terms of distributions.

As we will see it also allows for a natural incorporation of data, a circumstance of ever greater importance in a time of progressing digitalization of our lives, the medicine and the sciences coining the term big data.

We will furthermore tackle one of the main points of criticism on the Bayesian approach, namely its subjectivity in the choice of the prior: Two scientists, given the same data and working with the same model, can come up with different results (the posterior) imposing different a priori knowledge about the parameters in questions (the prior).

This critique lead to the school of objective Bayesian Analysis (c.f. [1]) with the goal to provide methods ensuring consistent results in repeated usage by scientists.

One approach is the choice of so called *non-informative priors*, using information theoretic considerations to formalize the notion of non-informativity, given rise to the *Jeffrey's prior* [12] and it's generalization to more general spaces, the *reference priors* [3].

An alternative approach is given by the empirical Bayes methods:

The empirical Bayes approach to statistical decision problems is applicable when the same decision problem presents itself repeatedly and independently with a fixed but unknown a priori distribution of the parameter - Herbert Robbins [16].

Here repeated measurements of the population in question, called cohort data, are used

to construct a prior representing that population. The first major contribution was by Robbins[15], suggesting the nonparametric maximization of the marginal likelihood, leading to the NPMLE estimator, but the topic got largely neglected, probably due to its computational cost, until the topic was brought back to attention in the parametric case by Efron and Morris [5] in 1973.

Unfortunately the NPMLE approach applied to finite data results in irregular priors, consisting of finitely many peaks.

In Section 3 we will therefore discuss its regularization. We start by treating the topic of penalization of unsmooth solution, leading to the MPLE estimate, and will set this into relation with Bayesian hyperpriors, i.e. prior assumption on the prior.

We then continue by introducing the *mutual information penalty*, a specific choice for penalizing unsmooth priors based on information theoretic considerations. We then end up with a nonparametric, hence generally applicable, method combining the assumptions of least information from the non-informative priors with the usage of cohort data from the empirical Bayes approach and therefore getting the best of both worlds. The suggested prior can as well be seen as a generalization of the reference priors to the cohort data regime.

We additionally introduce the DS-MLE estimate by Seo and Lindsay [20], an alternative approach with the idea of tackling the problem of finite data at its root by smoothing the data itself followed by the regular maximum likelihood estimation.

In section 4 we will then address the question of how to compute the introduced prior estimates numerically. We will work with a sample driven Monte Carlo approach, expressing the priors as importance samplings. We then derive the explicit formulas for the EM-algorithm for the approximation of the NPMLE and the DS-MLE and provide the jacobian for the optimization of the MPLE with the *mutual information penalty*.

We conclude the section with a digression to Markov Chain Monte Carlo sampling used for the computation of the Monte Carlo discretization.

Finally we will apply the developed methods and algorithms to a high-dimensional model from systems biology and discuss the results in section 5.

## 2 Empirical Bayes Methods

### 2.1 The Bayesian formalism

We start by laying out the basic formal tools in the Bayesian setting.

**Definition 1.** Let  $X$  and  $Y$  denote continuous random variables and  $\rho_{X,Y}(x, y)$  their joint probability density. The *conditional probability* density of  $Y$  given the value  $x$  for  $X$  is

$$\rho_{Y|X}(y|x) := \frac{\rho_{X,Y}(x, y)}{\rho_X(x)},$$

where  $\rho_X(x)$  is the *marginal density* of  $X$  defined as the joint density  $\rho(x, y)$  marginalized over all possible  $y$ :

$$\rho_X(x) := \int_y \rho(x, y) dy.$$

Whenever the corresponding random variables are clear we will, by slight abuse of notation, directly denote the condition in the subscript, i.e.

$$\rho_{Y|x}(y) := \rho_{Y|X}(y | x).$$

Successive insertion of these identities leads to *Bayes' theorem* in its probability density form:

$$\rho_{X|y}(x) := \frac{\rho_{X,Y}(x, y)}{\rho_Y(y)} = \frac{\rho_{Y|x}(y) \rho_X(x)}{\rho_Y(y)} = \frac{\rho_{Y|x}(y) \rho_X(x)}{\int_x \rho_{Y|x'}(y) \rho_X(x') dx'}. \quad (2.1)$$

This formula, constituting the heart of Bayesian statistics, tells us how to reconstruct the *posterior distribution*  $\rho_{X|y}$  of the unknown parameter  $x$  given data  $y$ , using the *likelihood*  $\rho_{Y|x}(y)$  of  $x$  given  $y$  as well as the *prior*  $\rho_X(x)$  reflecting our prior assumptions on the density of  $X$ .

Note that for fixed  $y$  the posterior  $\rho_{X|y}$  and prior  $\rho_X(x)$  both are probability densities in  $x$ . The likelihood on the other side is not a probability density in  $x$  (it would be one in  $y$  for fixed  $x$ ). For this reason it is also called the *likelihood function*

$$L(x | y) := \rho_{Y|x}(y).$$

## 2.2 The likelihood model

Our inference bases on the combination of a deterministic physical model, our description of the reality, with a stochastic measurement error and the formalism of Bayes'. The physical model is represented as a map  $\Phi : \mathcal{X} \subseteq \mathbb{R}^n \rightarrow \mathcal{Y} \subseteq \mathbb{R}^m$ , mapping some parameter  $x \in \mathcal{X}$  to a resulting state  $y \in \mathcal{Y}$ . We furthermore model the the data generating measurement process  $Z$  as an independent Gaussian perturbation with prescribed covariance  $\Sigma$  of that state:

$$\rho_{Z|X}(z | x) = \Phi(x) + E, \quad E \sim \mathcal{N}(0, \Sigma) \quad (2.2)$$

or slightly abusing notation

$$Z | X \sim \mathcal{N}(\Phi(X), \Sigma),$$

where  $\mathcal{N}(y, \Sigma)$  denotes the Normal distribution with mean  $y$  and covariance matrix  $\Sigma$ .

This *likelihood model* gives us the means to compute the probabily of measuring a single measurement  $z$ , given the underlying parameter  $x$ .

Assuming the *prior distribution* on  $X$  was known, this would enable us to compute the *posterior*  $\rho_{X|z}$  given some measurement  $z$  by straightforward application of the Bayes' theorem (2.1).

Note also that whilst this model is extensible to multiple measurements using the product of likelihoods as likelihood, this is only valid under the assumption of identically distributed likelihoods, which corresponds to the assumption that the same parameter  $x$  is underlying the different measurements. This would be the right model if all measurements result from the same realization of  $X$  (the same subject), but is wrong assuming different measurements correspond to independent draws from the prior  $X$  (multiple subjects).

## 2.3 The empirical Bayes model

Since in general the *prior*  $X$  cannot be assumed to be known, a number of different methods have been established for estimating this prior based on empirical cohort data, giving rise to the so called *empirical Bayes methods*. In that context we extend the model by conditioning the prior  $\rho_X$  on a hyperparameter  $\Pi$ , the prior of priors if one likes, resulting in the hierarchical model  $\Pi \rightarrow X \rightarrow Z$ , which we will refer to as the *hyperparametric model*.

Most literature confines itself to (finite dimensional) parametric empirical Bayes methods,

characterized by considering parametrized families of distributions for the priors, e.g.

$$\rho_{X|\pi} = \mathcal{N}(\pi, I), \pi \in \text{Im}(\Pi) = \mathbb{R}^n,$$

since these may admit explicit formulas for prior point estimates if the likelihood model and prior families admit simple forms, as well as circumventing regularization issues. We aim at a more general solution to the inference problem by allowing arbitrary distributions as priors, i.e.

$$\rho_{X|\pi} = \pi, \pi \in \text{Im}(\Pi) = \mathcal{M}_1(\mathcal{X}) := \{\rho \in L^1(\mathcal{X}) \mid \rho \geq 0, \|\rho\|_{L^1} = 1\},$$

resulting in a *nonparametric empirical Bayes* method.

The marginal likelihood of a prior  $\Pi = \pi$  given a single measurement  $z$  is then given by

$$L(\pi \mid z) = \rho_{Z|\pi}(z) = \int_{\mathcal{X}} \rho_{Z|x}(z) \pi(x) dx.$$

Since this likelihood, in contrast to the basic Bayesian model above, does not depend on a specific realization of the latent variable  $X$  anymore, this allows us to handle multiple measurements coming from independent samples of  $X$  correctly using the product distribution:

**Definition 2.** For finite data/measurements  $\mathbf{z}^M = (z_m \in \mathcal{Z})_{m=1,\dots,M}$  we define the likelihood of a prior  $\pi$  as

$$L(\pi \mid \mathbf{z}^M) := \prod_{m=1}^M \rho_{Z|\pi}(z_m)$$

or alternatively in its renormalized logarithmic form as *finite data log-likelihood*

$$\mathcal{L}(\pi \mid \mathbf{z}^M) := \frac{1}{M} \log \rho(\mathbf{z}^M | \pi) = \frac{1}{M} \sum_{m=1}^M \log \rho_{Z|\pi}(z_m).$$

For “infinite data/measurements”, represented in the form of a data-generating probability distribution  $\rho_Z$ , we define the corresponding *infinite data log-likelihood*

$$\mathcal{L}^\infty(\pi \mid \rho_Z) := \int_{\mathcal{Z}} \rho_Z(z) \log \rho_{Z|\pi}(z) dz.$$



The latter definition, also called the cross entropy between  $\rho_Z$  and  $\rho_{Z|\pi}$ , follows from the former in the limit for  $m \rightarrow \infty$  assuming that  $\rho_Z$  is indeed the data generating distribution:

$$z_m \stackrel{i.i.d.}{\sim} \rho_Z \Rightarrow \mathcal{L}(\pi | z^M) \xrightarrow[M \rightarrow \infty]{p} \mathcal{L}^\infty(\pi | \rho_Z). \quad (2.3)$$

The following proposition demonstrates how we can recover the data underlying “true prior”  $\pi^*$  in the infinite data regime by maximizing the corresponding likelihood functional  $L^\infty$ .

**Proposition 3.** *Let the hyperparametric model be well specified, i.e.*

$$\exists \pi^* \in \mathcal{M}_1(\mathcal{X}) : \rho_Z = \rho_{Z|\pi^*}$$

*and identifiable [23, chapter 5]*

$$\rho_{Z|\pi'} = \rho_{Z|\pi^*} \Rightarrow \pi' = \pi^* \quad \forall \pi' \in \mathcal{M}_1.$$

*We then have that*

$$\pi^* = \arg \max_{\pi' \in \mathcal{M}_1(\mathcal{X})} L^\infty(\pi').$$

*Proof.* Gibbs’ inequality says that

$$\int_{\mathcal{Z}} \rho_Z(z) \log \rho_Z(z) dz \geq \int_{\mathcal{Z}} \rho_Z(z) \log q(z) dz$$

for any probability density  $q$ , with equality if and only if  $q = \rho_Z$ . The rest follows from the assumptions.  $\square$

Both of the assumptions arise rather naturally; if the model is not well specified this merely means the measured data  $\rho_Z$  cannot be explained by any prior, thus resulting in an ill-posed problem. If on the other hand the model is not identifiable, which by definition corresponds to the injectivity of the marginal likelihood function  $\rho_Z$ , there exists another  $\pi' \neq \pi^*$  inducing the same measurements so we cannot hope to recover the right prior candidate from the data.

The latter problem can be retracted though by lifting the inference problem to equivalence classes of priors leading to the same measurements,

$$\pi \sim \pi' : \iff \|\rho_{Z|\pi} - \rho_{Z|\pi'}\|_{L^1(\mathcal{Z})} = 0, \quad (2.4)$$

which is all we can hope for.

In practice though usually only finite data is available, and even though the limiting property (2.3) might give hope that the NPMLE estimate

$$\pi_{ML} := \arg \max_{\pi' \in \mathcal{M}_1} \mathcal{L}(\pi' | \mathbf{z}^M)$$

might approximate  $\pi^*$  properly, one can prove [13, Theorem 21] that the maximizer of  $\mathcal{L}$  is a discrete distribution with at most  $M$  nodes.

In the field of machine learning this phenomenon, commonly occurring for insufficient data, is referred to as *overfitting* and usually approached by regularization techniques, methods to enforce more regular and smooth solutions.

## 3 Regularization

To address this problem of irregularity we will introduce two regularization methods, the *maximum penalized likelihood estimation* (MPLE), introducing a penalization term to the former optimization problem, and the *doubly smoothed maximum likelihood estimation* (DSMLE), lifting the problem from the finite to the infinite data regime by smoothing the measurements and thus approximating the continuous data-generating distribution  $\rho_Z$ .

### 3.1 Regularization via a penalization term

For a given likelihood function  $L$  and a *roughness penalty* (or *regularization term*)  $\Phi : \mathcal{M}_1 \rightarrow \mathbb{R}$ , responsible for penalizing unsmooth or unwanted solutions with high values, the MPLE estimate  $\pi_\Phi$  admits the form

$$\pi_\Phi = \arg \max_{\pi} \log L(\pi) - \Phi(\pi). \quad (3.1)$$

This approach also allows for an interpretation in the context of the Bayesian hyperparametric model by identifying the penalty  $\Phi$  with the hyperprior  $\Pi$  via  $\rho_\Pi \propto e^{-\Phi}$ . The posterior for  $\Pi$  is then

$$\rho_{\Pi|Z} \propto L(\pi) e^{-\Phi(\pi)}$$

and thus the *maximum a posteriori* estimate  $\pi_{MAP}$  for the hyperparametric model corresponds to the MPLE estimate:

$$\pi_{MAP} = \arg \max_{\pi} L(\pi) e^{-\Phi(\pi)} = \arg \max_{\pi} \log L(\pi) - \Phi(\pi) = \pi_\Phi.$$

One now might argue that we started with the question of finding the correct prior and just complicated the situation by transferring this problem to the question of the correct hyperprior. While this may be true we argue that the latter can be tackled from a rather abstract, problem independent standpoint, hence leading to a more general answer.

### 3.2 An information theoretic penalty

Many of the common penalty functions currently in use, penalizing either large amplitudes (e.g. ridge regression [14, section 1.6]) or derivatives (c.f. [9]) of the prior, are not invariant under reparametrizations of the parameter space  $\mathcal{X}$  and are rather ad-hoc without a natural derivation. Following a more information-theoretic view Good [8] suggested the use of the differential entropy for the penalty

$$\Phi_{H_X}(\pi) := \gamma \int_{\mathcal{X}} \rho_{X|\pi}(x) \log \rho_{X|\pi}(x) dx,$$

with  $\gamma \in \mathbb{R}^+$ , the regularization constant, determining the degree of smoothing due to this penalty. This prior however is still variant under reparametrizations of  $\mathcal{X}$  due to the log-nonlinearity. This means that if two scientists estimate the prior using equivalent models, using different systems of units, they could end up with different estimates. Hence this penalty does not rectify the problem of subjectivity in the Bayesian method. We therefore look for a penalty which is invariant under coordinate transformations.

Embracing the information theoretic approach we therefore propose the use of the *mutual information* instead of the entropy for the penalty:

**Definition 4.** Let  $A : \Omega \rightarrow \mathcal{A}$  and  $B : \Omega \rightarrow \mathcal{B}$  be two continuous random variables,  $\rho_{A,B}$  their joint probability density and  $\rho_A, \rho_B$  their respective marginal densities. Their mutual information is defined as

$$\begin{aligned} \mathcal{I}(A; B) &:= \int_{\mathcal{A}} \int_{\mathcal{B}} \rho_{A,B}(a, b) \log \left( \frac{\rho_{A,B}(a, b)}{\rho_A(a) \rho_B(b)} \right) da db \\ &= \mathbb{E}_{b \sim B} [D_{KL}(\rho_{A|b} \parallel \rho_A)] \\ &= H(B) - H(B; A), \end{aligned}$$

with  $D_{KL}$  being the *Kullback-Leibler divergence* from  $\rho_A$  to  $\rho_{A|b}$

$$D_{KL}(\rho_{A|b} \parallel \rho_A) := \int_{\mathcal{A}} \rho_{A|b}(a) \log \frac{\rho_{A|b}(a)}{\rho_A(a)} da,$$

and  $H(B)$ ,  $H(B; A)$  being the *differential entropy* of  $B$  respectively the *conditional differential entropy* of  $B$  given  $A$

$$\begin{aligned} H(B) &:= - \int_{\mathcal{B}} \rho_B(b) \log(\rho_B) db \\ H(B; A) &:= \int_{\mathcal{A}} \rho_A(a) H(B | a) da \\ &= - \int_{\mathcal{A}} \rho_A(a) \int_{\mathcal{B}} \rho_{B|a}(b) \log(\rho_{B|a}) db da. \end{aligned}$$

The mutual information quantifies the “amount of information” that one random variable shares with the respective other, expressed by the information content of the their joint distribution  $(\rho_{A,B})$  relative to their joint distribution if they were independent  $(\rho_A \rho_B)$ , weighted by their joint distribution.

We can gain further insights into its meaning by expressing it in terms of another fundamental information-theoretic quantity, the Kullback-Leibler divergence  $D_{KL}(A \| B)$  from  $B$  to  $A$  (also called *information gain* or *relative entropy*). It is a measure for the loss of information when considering  $B$  as a approximation to  $A$ , or consequently in the Bayesian context it is the gain of information revising one’s beliefs from the prior  $B$  to the posterior  $A$ .

In this form the mutual information of  $A$  and  $B$  corresponds to the expected information gain from the prior to the posterior over  $A$  when the measurements are  $B$ -distributed. This interpretation gives rise to the following definition:

**Definition 5.** For  $\gamma > 0$  constant we define the *information penalty*

$$\begin{aligned} \Phi_I^\gamma(\pi) &:= -\gamma \mathcal{I}(X | \pi; Z | \pi) \\ &= -\gamma \int_{\mathcal{X}} \rho_{X|\pi}(x) \int_{\mathcal{Z}} \rho_{Z|x}(z) \log\left(\frac{\rho_{Z|x}(z)}{\rho_{Z|\pi}(z)}\right) dz dx. \end{aligned} \quad (3.2)$$

Minimizing this penalty then corresponds to maximizing the amount of shared information between the prior-predictive distribution  $Z | \pi$  and the prior  $X | \pi$  itself (where we understand these random variables as restrictions of  $Z$  respectively  $X$  onto the events where  $\Pi = \pi$ ). In terms of the Kullback-Leibler formulation this means priors  $\pi$  are rewarded by the amount of information gain expected from their induced measurements, hence encoding a notion of non-informativity.

Fortunately the mutual information is also transformation invariant, thus allowing for the application of the information penalty independent of the models parametrization:

**Lemma 6.** *Let  $A, B$  as above, and  $\varphi^{-1} : \mathcal{A} \rightarrow \tilde{\mathcal{A}}, \psi^{-1} : \mathcal{B} \rightarrow \tilde{\mathcal{B}}$  be diffeomorphisms defining the coordinate transformations and corresponding transformed random variables  $\tilde{A}, \tilde{B}$  with the densities*

$$\begin{aligned}\rho_{\tilde{A}, \tilde{B}}(\tilde{a}, \tilde{b}) &:= \rho_{A, B}(\varphi(\tilde{a}), \psi(\tilde{b})) |D\varphi(\tilde{a})| |D\psi(\tilde{b})| \\ \rho_{\tilde{A}}(\tilde{a}) &:= \rho_A(\varphi(\tilde{a})) |D\varphi(\tilde{a})|, \quad \rho_{\tilde{B}}(\tilde{b}) := \rho_B(\psi(\tilde{b})) |D\psi(\tilde{b})|.\end{aligned}$$

The mutual information  $\mathcal{I}(A; B)$  is then invariant under these coordinate transformations of  $\mathcal{A}$  and  $\mathcal{B}$ :

$$\mathcal{I}(A; B) = \mathcal{I}(\tilde{A}; \tilde{B}).$$

*Proof.* According to the change of variables formula

$$\begin{aligned}\mathcal{I}(A; B) &= \int_{\mathcal{B}} \int_{\mathcal{A}} \rho_{A, B}(a, b) \log \left( \frac{\rho_{A, B}(a, b)}{\rho_A(a) \rho_B(b)} \right) da db. \\ &= \int_{\tilde{\mathcal{B}}} \int_{\tilde{\mathcal{A}}} \rho_{A, B}(\varphi(\tilde{a}), \psi(\tilde{b})) \log \left( \frac{\rho_{A, B}(\varphi(\tilde{a}), \psi(\tilde{b}))}{\rho_A(\varphi(\tilde{a})) \rho_B(\psi(\tilde{b}))} \right) |D\varphi(\tilde{a})| |D\psi(\tilde{b})| d\tilde{a} d\tilde{b} \\ &= \int_{\tilde{\mathcal{B}}} \int_{\tilde{\mathcal{A}}} \rho_{\tilde{A}, \tilde{B}}(\tilde{a}, \tilde{b}) \log \left( \frac{\rho_{\tilde{A}, \tilde{B}}(\tilde{a}, \tilde{b})}{\rho_{\tilde{A}}(\tilde{a}) \rho_{\tilde{B}}(\tilde{b})} \right) d\tilde{a} d\tilde{b} \\ &= \mathcal{I}(\tilde{A}; \tilde{B})\end{aligned}$$

□

**Corollary 7.** *The maximum penalized likelihood estimator  $\pi_{\Phi_I^\gamma}$  (3.1) with the information penalty  $\Phi_I^\gamma$  (3.2) is invariant under the transformations of  $\mathcal{X}$  and  $\mathcal{Y}$  specified in Lemma 6.*

In the case of an additive measurement error we can simplify the MPLE estimator by only computing the entropy of the prior predictive distribution:

**Theorem 8.** *For models with additive measurement error  $E \sim \rho_E$*

$$Z = G(X) + E$$

*the MPLE estimate  $\pi_{\Phi_{H_Z}^\gamma}$ , penalized by the Z-entropy*

$$\Phi_{H_Z}^\gamma(\pi) := -\gamma H(Z | \pi),$$

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and the information penalty coincide:

$$\pi_{\Phi_I^\gamma} = \pi_{\Phi_{H_Z}^\gamma}.$$

*Proof.* In the case of additive measurement error  $\rho_{Z|x}$  consists of shifts of  $\rho_E$

$$\rho_{Z|x}(z) = \rho_E(z - G(x))$$

and thus

$$\begin{aligned} H(Z | x) &= \int_{\mathcal{Z}} \rho_{Z|x}(z) \log(\rho_{Z|x}(z)) \, dz \\ &= \int_{\mathcal{Z}} \rho_E(z) \log(\rho_E(z)) \, dz \\ &= H(E). \end{aligned}$$

Hence the conditional entropy part is constant and both penalties agree up to an additive constant

$$\begin{aligned} \Phi_I^\gamma(\pi) &= -\gamma(H(Z | \pi) - H(Z; X | \pi)) \\ &= -\gamma\left(H(Z | \pi) - \int_{\mathcal{X}} \rho_{X|\pi}(x) H(Z | x) \, dx\right) \\ &= -\gamma(H(Z | \pi) + H(E)) \\ &= \Phi_{H_Z}^\gamma + \gamma H(E). \end{aligned}$$

Therefore their maxima agree and the estimates are the same.  $\square$

*Remark 9.* For the mentioned additive error model and discrete parameter space  $\mathcal{X}$ , Klebanov et al. [?, 3.1] show that the hyperprior  $\rho_\Pi(\pi) \propto \exp H(Z | \pi)$  maximizes the total entropy  $H(Z, \Pi)$  of the whole model and furthermore conjecture this to hold as well for continuous  $\mathcal{X}$ . This derivation from a maximum entropy principle is a further justification for the choice of  $\Phi_{H_Z}^\gamma$  as a meaningful penalty.

*Remark 10.* In the case of no data  $\mathbf{z}^M$  the likelihood term of  $\pi_{\Phi_I^\gamma}$  vanishes. It then matches the definition of reference priors [2] by Beger et al. Therefore this estimation routine can be seen as an extension of reference priors from a noninformative to a cohort-data based empirical Bayes approach.

*Remark 11.* It can be shown that the information penalty is convex in  $\pi$ , with strict

convexity in the identifiable case. Together with convexity of the likelihood function  $L$ , the MPLE (3.1) becomes a concave optimization problem.

### 3.3 Regularization by smoothing of the data

Instead of relying on the coarse approximation of the data generating distribution by the empirical distribution  $\rho_{\mathbf{z}^M} := \frac{1}{M} \sum_{m=1}^M \delta_{z_m} \approx \rho_Z$  and then penalizing overconfident priors, we may as well address the issue of overfitting by using a smooth approximation  $\tilde{\rho}_{\mathbf{z}^M}$  to  $\rho_{\mathbf{z}^M}$ .

In the following we will apply the idea of smoothing the data by a kernel convolution, introduced by Seo and Lindsay [20] as the *doubly-smoothed maximum likelihood estimator* (DS-MLE), to the empirical Bayes setting.

**Definition 12.** Let  $K : \mathcal{Z} \rightarrow \mathbb{R}$  be a kernel density function and  $\mathbf{z}^M = (z_m \stackrel{i.i.d.}{\sim} \rho_Z)_{m=1}^M$  be  $M$  measurements. The *smoothed data density* is then defined as

$$\tilde{\rho}_{\mathbf{z}^M}(z) = (\rho_{\mathbf{z}^M} * K)(z) := \frac{1}{M} \sum_{m=1}^M K(z - z_m).$$

Note that when smoothing the data we also have to smooth the model (hence *doubly smoothed*) to amount for the additional uncertainty in the data and stay consistent:

$$\tilde{\rho}_{\mathbf{z}^M} \xrightarrow{M \rightarrow \infty} \rho_Z * K = \tilde{\rho}_{Z|\pi^*} \neq \rho_{Z|\pi^*},$$

where  $\pi^*$  is the data-generating prior as in Proposition 3.

Hence the corresponding *smoothed likelihood model* is given by

$$\begin{aligned} \tilde{\rho}_{Z|x} &= \rho_{Z,x} * K \\ \Rightarrow \tilde{\rho}_{Z|\pi} &= \rho_{Z|\pi} * K \end{aligned}$$

The resulting DS-MLE then takes the form

$$\pi_{DS} := \arg \max_{\pi \in \mathcal{M}_1(\mathcal{X})} \mathcal{L}^\infty(\pi \mid \tilde{\rho}_{\mathbf{z}^M})$$

and is proved to be consistent under weak assumptions on the kernel and likelihood model (c.f. [20]).

Note however that the choice of a kernel  $K$  leaves space for debate. Furthermore this procedure is not invariant under reparametrizations of the measurement space  $\mathcal{Z}$  for fixed kernels. Hence this approach, although rather natural and simple does not remedy the problem of subjectivity in the Bayesian inference.

## 4 Numerical schemes

### 4.1 Monte Carlo approximations

Since the arising integrals are in general not tractable analytically, we will make use of sample based discretization of the continuous spaces  $\mathcal{X}$ ,  $\mathcal{Z}$  and use Monte Carlo integration for the corresponding integrals.

1. Given  $M$  measurements  $\mathbf{z}^M = (z_i)_{i=1}^M$  sampled across the population, these are distributed across the marginal measurement distribution  $z_i \sim \rho_Z$  by construction of the model. We can hence approximate

$$\rho_Z \approx \frac{1}{M} \sum_{m=1}^M \delta_{z_m}.$$

2. In the case of the parameter space  $\mathcal{X}$  we start with an arbitrary sampling  $\mathbf{x} = (x_k \in \mathcal{X})_{k=1}^K$  distributed according to some density  $x_i \sim \rho_X$ . We can now approximate any other density distribution  $\rho_Y$  on  $\mathcal{X}$  as an importance sampling with weights  $\mathbf{w} = (w_k)_{k=1}^K$ ,  $w_k \geq 0$ ,  $\sum_{k=1}^K w_k = 1$  such that  $w_i \propto \frac{\rho_Y(x_i)}{\rho_X(x_i)}$ . We then have

$$\rho_Y \approx \sum_{k=1}^K w_k \delta_{x_k}.$$

Approximating any prior  $\pi$  in terms of its weights  $w_k$ ,

$$\pi \approx \rho_{X|w} := \sum_{k=1}^K w_k \delta_{x_k}, \tag{4.1}$$



the prior predictive distribution can be approximated by

$$\begin{aligned}\rho_{Z|\pi}(z) &= \int_{\mathcal{X}} \rho_{Z|x}(z) \pi(x) dx \\ &\approx \rho_{Z|w}(z) := \sum_{k=1}^K w_k \rho_{Z|x_k}(z).\end{aligned}$$

Inserting this into the marginal likelihood leads to

$$L(\pi | \mathbf{z}^M) \approx L(\mathbf{w} | \mathbf{z}^M) := \prod_{m=1}^M \sum_{k=1}^K w_k \rho_{Z|x_k}(z_m).$$

In order to integrate over the density  $\rho_{Z|\pi}$  for the entropy hyperprior, we approximate its density by an additional weighted sampling consisting of  $\bar{K} > K$   $\mathcal{Z}$ -samples generated from the given  $\mathcal{X}$ -sampling by

$$\bar{\mathbf{z}} := \left( \bar{z}_j \sim \rho_{Z|x_{J(j)}} \right)_{j=1}^{\bar{K}}$$

with corresponding weights

$$\bar{w}_j := \frac{w_{J(j)}}{\#J^{-1}(J(j))}.$$

Here  $J : \{1, 2, \dots, \bar{K}\} \rightarrow \{1, 2, \dots, K\}$  denotes a surjective index mapping function, mapping from the  $\mathcal{Z}$ - to the corresponding  $\mathcal{X}$ -samples indices. The normalizing factor in the weights amounts for the inflation by multiple  $\mathcal{Z}$ -samples  $\bar{z}_i, \bar{z}_j$  from a single  $\mathcal{X}$ -sample in the case of  $J(i) = J(j)$ .

The Monte Carlo approximation to the  $\mathcal{Z}$ -entropy then takes the form

$$H(Z | \pi) \approx H(Z | \mathbf{w}) := -\gamma \sum_{j=1}^{\bar{K}} \bar{w}_j \log \left( \sum_{k=1}^K w_k \rho_{Z|x_k}(\bar{z}_j) \right).$$

We can furthermore approximate the expectation value of any measurable function  $g$  under  $\pi$  via

$$\mathbb{E}_{x \sim \pi} [g(x)] = \int_{\mathcal{X}} g(x) \pi(x) dx \approx \sum_{k=1}^K w_k g(x_k).$$

## 4.2 EM algorithm

We will now show

We will now show how to apply the well known *Expectation Maximization* (EM) algorithm for the NPMLE and DS-MLE.

Herefore let us first recapitulate the EM-algorithm following the classic paper of Dempster, Laird and Rubin [4].

We start by defining the *complete data likelihood function*

$$L^c(\tilde{\mathbf{x}}, \tilde{\mathbf{z}} \mid \pi) := \prod_{m=1}^M \rho_{X|\pi}(\tilde{x}_m) \rho_{Z|\tilde{x}_m}(\tilde{z}_m),$$

the likelihood of a specific prior represented by  $w$  given the measurements  $\tilde{\mathbf{z}} = (\tilde{z}_m)_{m=1}^M$  as well as the parameters  $\tilde{\mathbf{x}} = (\tilde{x}_m)_{m=1}^M$ , where the completeness is meant in the context of knowing all involved variables, including  $\tilde{\mathbf{x}}$ .

Based on this we define the *expected complete data log-likelihood* of  $\pi$  with respect to the current estimate  $\pi_n$  as the expectation of the logarithm of the complete data likelihood over  $X$  conditioned on the estimate  $\pi_n$  and the cohort-data  $\mathbf{z}^M$ :

$$\begin{aligned} Q(\pi \mid \pi_n) &:= \mathbb{E}_{\mathbf{X}_n} [\log(L^c(\mathbf{X}, \mathbf{z}^M \mid \pi))], \\ &= \mathbb{E}_{\mathbf{X}_n} \left[ \sum_{m=1}^M \log(\rho_{X|\pi}(\tilde{x}_m) \rho_{Z|\pi}(\tilde{z}_m)) \right] \\ &= \sum_{m=1}^M \mathbb{E}_{x \sim \rho_{X|\pi_n, z_m}} [\log(\rho_{X|\pi}(x) \rho_{Z|x}(z_m))] \end{aligned} \tag{4.2}$$

where  $\mathbf{X}_n = \left( \tilde{x}_m \stackrel{\text{i.i.d.}}{\sim} \rho_{X|\pi_n, z_m} \right)_{m=1}^M$ . The second step follows from the insight that after exchanging integration and summation each log term depends only on a single  $x_m$  and hence the other  $x_m$ 's get marginalized out.

The EM algorithm works by iteratively maximizing the expected complete-data log-likelihood under the current estimate  $\pi_n$ :

$$\pi_{n+1} := \arg \max_{\pi \in \mathcal{W}} Q(\pi \mid \pi_n).$$

For a proof of uniqueness and convergence in the case of strict convex likelihoods we refer to [4] and [24].

## 4 NUMERICAL SCHEMES

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Let us compute the corresponding formulas for our Monte Carlo approximations.

For the approximations (4.1) of  $\pi$  and  $\pi_n$  in terms of  $\mathbf{w}$  and  $\mathbf{w}_n$  respectively

$$\begin{aligned}\pi &\approx \sum_{k=1}^K w_k \delta_{x_k}, \\ \pi_n &\approx \sum_{k=1}^K w_{n,k} \delta_{x_k}\end{aligned}$$

we have for any measurable function  $f$

$$\begin{aligned}\mathbb{E}_{x \sim \rho_{X|\pi_n, z_m}} [f(x)] &= \int_{\mathcal{X}} \rho_{X|\pi_n, z_m}(x) f(x) \, dx \\ &\approx \sum_{k=1}^K w_{n,k} \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|\mathbf{w}_n}(z_m)} f(x_k).\end{aligned}$$

Therefore we can approximate (4.2) by

$$\begin{aligned}Q(\pi \mid \pi_n) &\approx Q(\mathbf{w} \mid \mathbf{w}_n) := \sum_{m=1}^M \sum_{k=1}^K w_{n,k} \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|\mathbf{w}_n}(z_m)} \log(\rho_{X|\mathbf{w}}(x) \rho_{Z|x_k}(z_m)) \\ &= \sum_{m=1}^M \sum_{k=1}^K w_{n,k} \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|\mathbf{w}_n}(z_m)} \log(w_k \rho_{Z|x_k}(z_m)).\end{aligned}$$

We can furthermore explicitly compute the maximizer to the arising optimization problem

$$\mathbf{w}_{n+1} := \arg \max_{\mathbf{w} \in \mathcal{W}} Q(\mathbf{w} \mid \mathbf{w}_n),$$

where

$$\mathcal{W} := \mathcal{M}_1(\{1, \dots, K\}).$$

A necessary condition is that the gradient at  $\mathbf{w}$  is orthogonal to the tangent space  $T_{\mathbf{w}}\mathcal{W}$

of  $\mathcal{W}$ , which means that all components of the gradient are the same:

$$\begin{aligned} \frac{dQ(\mathbf{w} \mid \mathbf{w}_n)}{dw_k} &\perp T_{\mathbf{w}}\mathcal{W} \\ \Rightarrow \exists c \in \mathbb{R} \forall k = 1, \dots, K : \\ \frac{dQ(\mathbf{w} \mid \mathbf{w}_n)}{dw_k} &= \sum_{m=1}^M \frac{w_{n,k}}{w_k} \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|w_n}(z_m)} = c \\ \Rightarrow w_k &= \frac{w_{n,k}}{c} \sum_{m=1}^M \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|w_n}(z_m)}. \end{aligned}$$

Since  $\sum_k w_k = 1$  we conclude  $c = 1/M$  and hence end up with the explicit EM step  $\mathbf{w}_{n+1} = \psi(\mathbf{w}_n)$ :

$$\psi(\mathbf{w}_n)_k := \frac{w_{n,k}}{M} \sum_{m=1}^M \frac{\rho_{Z|x_k}(z_m)}{\rho_{Z|w_n}(z_m)}.$$

Iterative application of this formula henceforth converges to the weights approximating the desired NPMLE estimate  $\pi_{ML}$ .

Applying the Monte Carlo discretization to the DS-MLE setting ([20]) we end up with the same EM-algorithm of the NPMLE applied to the augmented data points  $z_m \stackrel{i.i.d}{\sim} \tilde{\rho}_{\mathbf{z}^M}$  and the smoothed likelihoods (c.f. Section 3.3). Since  $M$  data points result in maximally  $M$  peaks in the NPMLE [13], a necessary condition for strictly positive weights is that the number of augmented data points is at least that of the parameter-space nodes,  $M > K$ .

### 4.3 Optimization for MPLE

In the case of additive the measurement error the Monte Carlo discretized version of the MPLE with the information penalty takes the form

$$w_{\Phi_I^\gamma} = \arg \max_{\mathbf{w} \in \mathcal{W}} O(\mathbf{w})$$

with objective function

$$\begin{aligned} O(w) &= \log L(\mathbf{w} \mid \mathbf{z}^M) - H(Z \mid \mathbf{z}^M) \\ &= \log \prod_{m=1}^M \sum_{k=1}^K w_k \rho_{Z|x_k}(z_m) + \gamma \sum_{j=1}^{\bar{K}} \bar{w}_j \log \left( \sum_{k=1}^K w_k \rho_{Z|x_k}(\bar{z}_j) \right). \end{aligned}$$

Being a composition of linear and concave functions the objective  $O$  is easily shown to be concave, allowing for the use of constraint concave/convex optimization routines.

The high dimensionality of  $\mathbf{w}$  suggests the usage of derivative based optimization techniques. The derivative of the objective is given by

$$\begin{aligned} \frac{dO}{dw_k}(w) &= \frac{\sum_{m=1}^M \rho_{Z|x_k}(z_m)}{\prod_{m=1}^M \sum_{k=1}^K w_k \rho_{Z|x_k}(z_m)} \\ &\quad + \gamma \sum_{j=1}^K \frac{\bar{w}_j \rho_{Z|x_k}(\bar{z}_j)}{\sum_{k=1}^K w_k \rho_{Z|x_k}(\bar{z}_j)} \\ &\quad + \gamma \sum_{j \in J^{-1}(k)} \frac{\log\left(\sum_{k=1}^K w_k \rho_{Z|x_k}(\bar{z}_j)\right)}{\#J^{-1}(k)}. \end{aligned}$$

*Remark.* Instead of first discretizing and then deriving, one might as well try to work with the discretization of the derivative (of the corresponding continuous objective). Whilst this promises to better approximate the gradient of the underlying continuous problem, the gradient does not fit to the objective anymore and may therefore lead to problems with optimization routines relying on correctness of the gradient.

#### 4.4 Markov Chain Monte Carlo

The quality of the Monte Carlo approximations greatly depends on the choice of the importance samples  $\mathbf{x}$ . Whilst an equidistant grid may work well for small dimensional parameter spaces  $\mathcal{X}$ , its number of samples/gridpoints increases exponentially with the dimension of  $\mathcal{X}$ . This so called curse of dimensionality suggests the use of Markov Chain Monte Carlo (MCMC) sampling, a popular sampling scheme for probability densities  $f$  defined over high-dimensional spaces.

The basic idea of MCMC methods revolves around constructing an ergodic Markov Chain, a stochastic process whose conditional probability for future states depends only on the current state, which has the desired target density  $f$  as stationary density. In the limit of infinite sample sizes the samples from the Markov Chain then are distributed according to  $f$ .

The probably most common MCMC scheme is the Metropolis–Hastings (MH) algorithm. It works by iteratively sampling a proposal  $x'_n \in \mathcal{X}$  around the last MCMC sample  $x_{n-1}$  according to a prescribed *proposal density*  $Q(x'_n | x_{n-1})$  and accepting or rejecting that proposal in such a way that the resulting MCMCs stationary distribution is  $f$ .

Let us define the corresponding Markov process in terms of its *transition probabilities*  $P(x_{n+1} | x_n)$ , starting from the detailed balance condition

$$\begin{aligned} P(x' | x) P(x) &= P(x | x') P(x') \\ \Leftrightarrow \frac{P(x)}{P(x')} &= \frac{P(x | x')}{P(x' | x)}, \end{aligned}$$

which ensures the existence of a stationary distribution  $\pi = P\pi$ .

Taking the Ansatz of splitting the transition probability into a proposal distribution  $g$  and an acceptance distribution  $A$

$$P(x' | x) = g(x' | x) A(x' | x),$$

we end up with

$$\frac{A(x' | x)}{A(x | x')} = \frac{P(x') g(x | x')}{P(x) g(x' | x)}. \quad (4.3)$$

The Metropolis-Hastings choice for the acceptance distribution

$$A(x' | x) := \min\left(1, \frac{P(x') g(x | x')}{P(x) g(x' | x)}\right)$$

satisfies this equation, since either  $A(x' | x)$  or  $A(x | x')$  is 1, while the other equals the desired right hand side of (4.3).

This choice allows for the formulation of the following theorem.

**Theorem 13.** *Let  $f, g \in \mathcal{M}_1(\mathcal{X})$  with  $f(x) > 0, g(x) > 0 \forall x \in \mathcal{X}$ . Then the Markov Process defined by*

$$P(x' | x) = g(x' | x) \min\left(1, \frac{f(x') g(x | x')}{f(x) g(x' | x)}\right)$$

*admits  $f$  as unique stationary distribution*

$$f = Pf.$$

*Proof.* That  $f$  indeed is a stationary distribution follows by construction, uniqueness follows from irreducibility which is given due to positivity of  $P$ .  $\square$

We hence can use this Markov Process to sample a Markov Chain according to the MH-MCMC algorithm:

1. Start from an arbitrary point  $x_0$
2. Sample a proposal state  $x'_{n+1} \sim g(x_{n+1} | x_n)$
3. With probability  $A(x'_{n+1} | x_n)$  set  $x_{n+1} := x'_{n+1}$ , otherwise set  $x_{n+1} := x_n$
4. Resume with 2 until sufficient states were generated

The speed of convergence to the stationary distribution is strongly influenced by the choice of the proposal distribution. Whilst sampling from proposals directly from the target distribution would lead to the best results, this process was not possible firsthand which is why we resorted to MCMC. A common choice for the proposal distribution is the normal distribution, but even here the choice of the covariance is vital for rapid mixing of the resulting Markov Chain.

To circumvent the obstacle of choosing a proper proposal covariance we decided to use the adaptive Metropolis (AM) algorithm by Haario et. al [10] which tunes the proposal covariance online based on the current samples, according to

$$\begin{aligned}
g_n(\cdot | x_n) &= \mathcal{N}(x, \Sigma_0) && \text{if } n \leq 2d, \\
g_n(\cdot | x_n) &= (1-\beta)\mathcal{N}\left(x, \frac{2.38^2}{d}\Sigma_n\right) + \beta\mathcal{N}(x, \Sigma_0) && \text{if } n > 2d,
\end{aligned}$$

with  $d$  beeing the dimensionality of the sampling space  $\mathcal{X}$  and  $\frac{2.38^2}{d}$  a scaling constant considered to be optimal for large dimensions [17].  $\Sigma_n$  is the covariance estimate based on the previous samples  $(x_i)_{i=0}^n$ , which can be computed recursively, and  $\Sigma_0$  an initially chosen positive definite covariance. The linear combination of the fixed normal by  $\beta > 0$  ensures that the resulting proposal covariance stays positive definite even in the case of singular  $\Sigma_n$ .

The acceptance step remains the same as with the standard MH-MCMC. This Markov Chain still admits the desired target density as stationary distribution, assuming it is log-concave outside of some arbitrary region (for a proof see [18]).

## 5 Application

We will now discuss the application of the developed empirical Bayes method on the basis of a large-dimensional ordinary differential model accompanied by real-life measurements. We will therefore introduce the model and obtain a discretization of  $\mathcal{X}$  by sampling from the individual Bayesian posteriors by means of MCMC sampling. We will then compute the MLE, MPLE and DS-MLE prior estimates and discuss the results.

### 5.1 The problem

Our physical model, consisting of a system of 33 ordinary differential equations, models the feedback mechanisms of the prevalent hormones in the female menstrual cycle with a focus on GnRH-receptor binding and was derived by Röblitz et al. [19]. For the defining equations we refer to the original paper.

This system is parametrized by 114 parameters, out of which 21 (the Hill parameters) are considered fixed for the following survey. In [19] the authors provide point estimates for the parameters and initial conditions, although concluding that only 52 of the parameters were identifiable. We will denote these as *nominal parameters*  $\theta^{nom}$  and *initial conditions*  $y_0^{nom}$  and use them as initial conditions for the Markov chain as well as for the prior computation.

Let us denote its solution at time  $t$  with parameters  $\theta \in \mathbb{R}^{82}$  and initial conditions  $y_0 \in \mathbb{R}^{33}$  as

$$\phi(t; \theta, y_0) \in \mathbb{R}^{33}.$$

Our data consists of blood concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and progesterone (P4) measured from 53 healthy women over thirty days, roughly every second day. This data was collected in the context of PAEON, a collaborative European research project on eHealth. Denote the set of measurements for a single patient  $m$

$$z^m := (z_{t,i}^m)_{(t,i) \in I_z^m}$$

with  $z_{t,i}^m$  being the single measurement of species  $i = 1, \dots, 4$  at time  $t$  and  $I_z^m$  denoting the index set of available measurements.

To impose the condition of periodicity of the data onto our inference process we further augment the data by a copy of itself shifted in time by an additional latent parameter representing the period length  $\tau$ :

$$z^{m,\tau} := (\hat{z}_{t,i}^m)_{(t,i) \in I_z^{m,\tau}},$$

with augmented index set

$$I_z^{m,\tau} = \bigcup_{(t,i) \in I_z^m} \{(t,i), (t+\tau, i)\}$$



and augmented measurements

$$\hat{z}_{t,i}^m := \begin{cases} z_{t,i}^m & \text{if } (t,i) \in I_z^m \\ z_{t-\tau,i}^m & \text{otherwise} \end{cases}.$$

Subsuming the latent model parameters  $\theta$  (82), the initial conditions  $y_0$  (33) and the period length  $\tau$  we end up with 116 parameters  $x = (\theta, y_0, \tau)$  for the Bayesian inference.

We model each single measurement as independent on the others and afflicted by a Gaussian measurement error with independent componentwise standard deviations of 10% of their respective order of magnitude, estimated from the nominal solution  $\phi^{nom}(t) := \phi(t; y_0^{nom}, \theta^{nom})$ :

$$\sigma_1^{\text{meas}} = 12, \sigma_2^{\text{meas}} = 1^2, \sigma_3^{\text{meas}} = 40^2, \sigma_4^{\text{meas}} = 1.5^2.$$

We end up with the following likelihood function for the parameters  $x$  given a single persons data  $z^m$ :

$$L(x \mid z^m) = L(\theta, y_0, \tau \mid z^m) = \left( \prod_{(t,i) \in I_z^{m,\tau}} \frac{1}{\sigma_i^{\text{meas}} \sqrt{2\pi}} \right) \exp \left( -\frac{1}{2} \sum_{(t,i) \in I_z^{m,\tau}} \left( \frac{\phi(t; \theta, y_0)_i - z_{t,i}^{m,\tau}}{\sigma_i^{\text{meas}}} \right)^2 \right).$$

*Remark 14.* This likelihood correctly reflects the amount of information available dependent on the number of measurements. A higher number of measurements results in sharper specified likelihood function. This will allow us to correctly treat different patients/measurements together in the upcoming empirical Bayes analysis.

*Remark 15.* One might argue that this model manipulates the data and hence is no more of the form (2.2). But it is equivalent to the model obtained but just duplicating the data and subsuming the shift operation into a new forward solution operator, hence Theorem 8 still applies.

For the initial Bayesian sampling procedure, necessary for arrival at a discretization of  $\mathcal{X}$ , we furthermore need to specify an initial prior  $\pi_0$  on our parameters.

*Remark 16.* For we did not want to imply any knowlege on  $\theta$  but their order of magnitude we chose the uniform prior bounded by the  $\alpha := 5$  multiple of its corresponding nominal parameter

$$X_i \mid \pi_0 = \mathcal{U}(0, \alpha \theta_i^{\text{nom}}) \quad i = 1, \dots, 82.$$

The prior for the initial conditions  $y_{0,i} = \theta_{82+i}$ ,  $i = 1, \dots, 33$  is constructed as a mixture of Gaussians centered at the trajectories of the nominal solution

$$X_{82+i} \mid \pi_0 := \frac{1}{31} \sum_{t=0}^{30} \mathcal{N}(\phi^{\text{nom}}(t), \Sigma) \quad i = 1, \dots, 33$$

and the covariance  $\Sigma$  being a diagonal matrix with the component-wise covariance estimates

$$\Sigma_{ii} := \text{Cov}\left((\phi_i^{\text{nom}}(t))_{t=0}^{30}\right), \quad i = 1, \dots, 33.$$

The prior for the period length  $\theta_{116}$  was chosen to be Gaussian with mean 28.9 days and a standard deviation of 3.4 days (c.f. [6])

$$X_{116} \mid \pi_0 := \mathcal{N}(28.9, 3.4^2).$$

## 5.2 Sampling

We will now compute the individual posterior samples

$$(x_i^m) \sim \rho_{x|z^m} L(\theta \mid z) \rho_z^0(z)$$

for each patient  $m$ .

Since all sampled parameters  $(\theta_i)_{i=1}^{116}$  are restricted to  $\mathbb{R}^+$  but the used AM sampler uses normal proposal densities with global support, we first rescale the original parameters using  $\log : \mathbb{R}^+ \rightarrow \mathbb{R}$ :

$$\tilde{\theta}_i = \log(\theta_i), \quad i = 1, \dots, 116.$$

The normal proposals in the log-space now correspond to lognormal proposals in the original parameter space.

However undergoing this transformation we also have to adjust the likelihood function according to the change of variables formula:

$$\tilde{L}(\tilde{\theta} \mid z) = L(\exp(\tilde{\theta}) \mid z) \prod_{i=1}^{116} \tilde{\theta}_i.$$

Choosing the initial value for the Markov chain according to our nominal values

$$\begin{aligned} x_{0,i} &:= \log \theta_i^{\text{nom}}, \quad i = 1, \dots, 82 \\ x_{0,82+i} &:= \log y_{0,i}^{\text{nom}}, \quad i = 1, \dots, 33 \\ x_{0,116} &:= \log 28.9, \end{aligned}$$

we may hope to start in a region of high density which henceforth is already representative for the target density and thus expect a relatively short burnin phase.

In the first runs the initial covariance  $\Sigma_0$  of the proposal density for the AM sampler was chosen to be uniform. Upon later runs we reused the covariance structure  $\Sigma_N$  of present samplings according to

$$\Sigma_0 := \frac{2.38^2}{d} \Sigma_n,$$

to speed up the adaption process.

We computed 50.000.000 samples  $\mathbf{x}^m$  of the individual posteriors  $\theta \mid \pi_0, z^m$  for each patient  $m$  at an average speed of around one million samples per hour and core, of which we rejected the first 10.000.000 as a burn-in phase.

We applied the convergence diagnostics by Gelman and Rubin[7] and concluded convergence of a parameter if the potential scale reduction factors 0.975 quantiles were estimated below 1.2. This lead to on average 74 converged parameters (varying per patient). The Heidelberger and Welch diagnostic [11] furthermore assessed componentwise stationarity of the Markov Chains for on average 109 parameters.

Keeping in mind that many of the parameters are probably unidentifiable (hence random walking in 100 dimensional space) we consider these as good results.

### 5.3 Prior estimation

After thinning the individual posterior samples  $(\mathbf{x}^m)_{m=1}^{53}$  for computational feasibility, we combined these in order to obtain a basis for the prior estimation.

$$\mathbf{x}^M = \bigcup_{m=1}^M \mathbf{x}^m.$$

The results below were computed with  $\#\mathbf{x} = 1325$ .

Note that these samples, which conform to the average density of the individual posteriors, are  $\psi(\pi_0)$  distributed. Our experiments have shown that this first approximation step is already quite close to the NPMLE. Since furthermore the MPLE is expected to be a smoothed version of the NPMLE, these points serve as a good basis for the importance sampling:

$$\mathbf{x} \sim \psi(\pi_0) \approx \pi_{ML} \approx \pi_{\Phi_I}^\gamma.$$

We computed the the NPMLE and DS-MLE estimates using 100 iterations of the EM algorithm, starting with uniform weights.

In case of the DS-MLE model we smoothed each data point  $z_i$  by 30 additional samples. The kernel  $K$  was chosen to be a multivariate Gaussian with diagonal covariance  $\Sigma^K$ , computed by Silverman’s rule of thumb[21] for kernel density bandwidth estimation, based on the individual data components:

$$\Sigma_{i,i}^K = 0.9M^{-\frac{1}{5}} \text{Cov}(z_i^m)_{m=1}^M.$$

For the optimization of the MPLE we used the Method of Moving Asymptotes algorithm [22], a globally-convergent, gradient-based optimizer. To guarantee the constraint  $\sum_{k=1}^K w_k = 1$  we used the built in Augmented Lagrangian algorithm. This basically amends a penalty to the objective, whose impact is scaled based on the current misfit of the constraint. We furthermore set the upper bounds for each component to 1, and the lower bounds to  $10^{-12}$  to avoid eventual divisions by zero.

The penalty constant  $\gamma$  is chosen by trial and error, until achieving desired smoothing results. It would be interesting to find a rule for its choice, e.g. by information theoretic reasons or cross validation.

## 5.4 Results

We will now compare the initial prior  $\pi_0$  with the NPMLE  $\pi_{ML}$ , the DS-MLE  $\pi_{DS}$  and the information penalized MPLE  $\pi_{\Phi_I}^\gamma$ . For the visualization we will plot kernel density estimates of selected marginal densities.

Figure 5.1 shows the marginal distributions of the individual priors, a density plot of the prior predictive distributions together with the cohort-data, and the resulting posteriors for a single person.

Figure ?? compares different choices for the regularization constant  $\gamma$  by showing the corresponding marginal distributions.

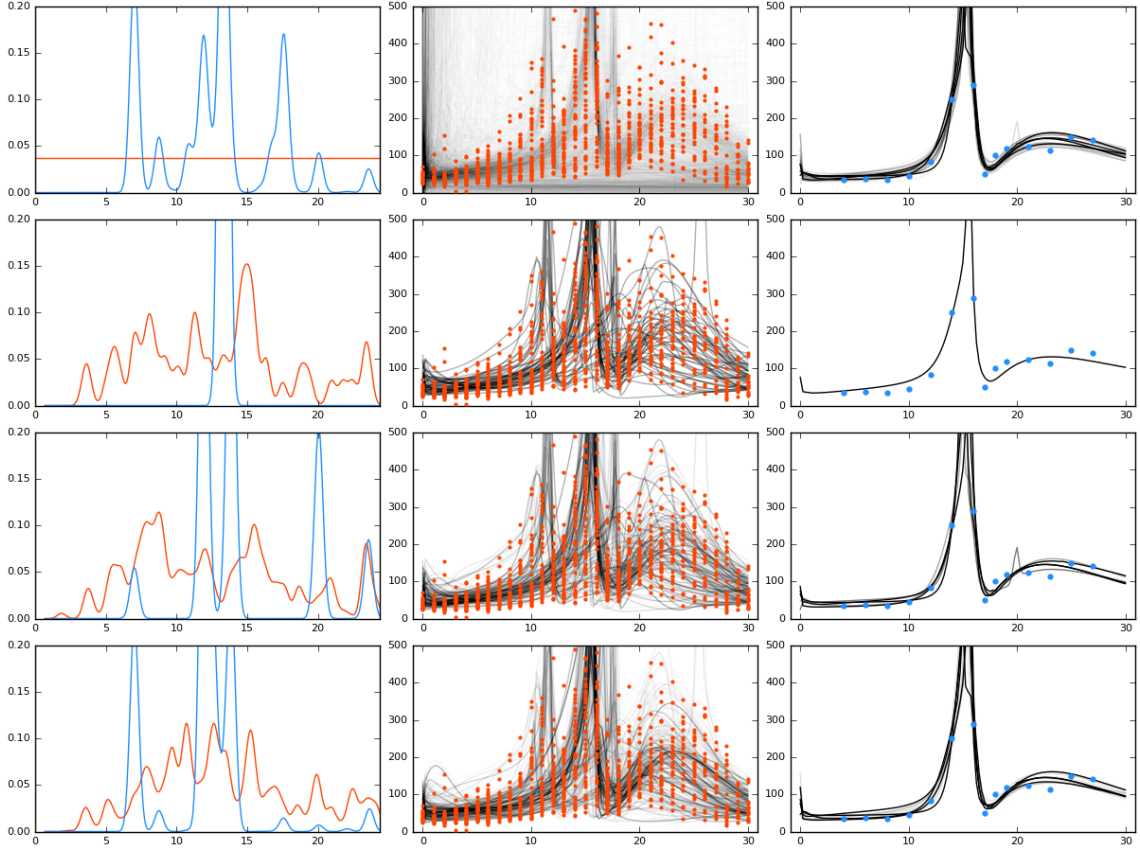


Figure 5.1: f

paperplot

2d marginals?

## 6 Conclusion

We have shown that the MPLE with the information penalty  $\Phi_I^\gamma$  is an attractive approach to the empirical Bayes method. It bases on natural, information theoretic considerations and admits the desirable property of transformation invariance, generalizing the notion of the reference priors to the empirical Bayes framework. Due to its concavity the objective is computationally manageable and its Monte Carlo approximation enables it's application to high-dimensional problems eluding the curse of dimensionality.

We furthermore showed how to apply the developed methods to a real world problem by the means of MCMC sampling.

Unfortunately we could not resolve all questions in the scope of this thesis. In my eyes

## 6 CONCLUSION

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the most important questions are how to speed up the optimization routine as well as the choice of the penalization constant  $\gamma$ .

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## Appendix

### Implementation

The introduced algorithms were implemented Julia, a modern programming language for numerical computing and bundled in the open-source package GynC.jl, available at [www.github.com/axsk/GynC.jl](http://www.github.com/axsk/GynC.jl).



For installation and usage run the following commands in the Julia REPL:

```
Pkg.clone("https://github.com/axsk/GynC.jl")
```

using GynC

In the following we will give an overview over the core components and methods of the software and mention some implementation details.

### Empirical Bayes

The core type of this module is the `LikelihoodModel(xs, ys, zs, datas, measerr, zsampledistr)`. It provides the base data necessary for the empirical Bayes methods.

- `xs`: vector of  $\mathcal{X}$ -samples ( $x_k$ )
- `ys`: corresponding pushforward under  $\Phi$
- `zs`: storage of additional  $z$  samples for  $z$ -entropy computation
- `datas`: vector of cohort measurements
- `measerr`: specification of the measurement error for likelihood computation
- `zsampledistr`: specification of the smoothing kernel  $K$  (DS-MLE only)

Based on this time the following convenience functions are available

`em(m::LikelihoodModel, w0, niter)`: perform `niter` iterations of the EM-algorithm on model `m`, starting with initial weights `w0`.

`mple(m::LikelihoodModel, w0, niter, reg, h)`: perform a constraint gradient ascent search to optimize the MPLE with  $\gamma = \text{reg}$ , initial weights `w0`, stepsize `h` and `niter` iterations.

`optimmple(m, reg, w0)`: perform a constraint optimization using the MMA optimizer

`hz(m,w)`, `dhz(m,w)`, `logl(m,w)`, `dlogl(m,w)`: compute the loglikelihood,  $z$ -entropies and their derivatives for the given weights `w`.

`smoothedmodel(m, mult)`: perform the smoothing of the data and likelihood functions for the DS-MLE.

`likelihoodmat(xs::Vector,ys::Vector,d::Distribution)`: compute the pairwise likelihoods based for a multivariate gaussian distribution `d`. This is an optimized version making use of the binomial decomposition and renormalization of the likelihoods for stability. It also handles incomplete data by excluding NaNs of the computations.

`gyncmodel(n)`: generate a `gync` likelihoodmodel with `n` presampled  $x$ -samples.

`gyncmodel(xs, datas; zmult, sigma)`: generate a `gync` likelihoodmodel for the given samples and `datas` with `zmult`  $z$  samples (for the entropy) per  $x$  sample and measurement error

standard deviation  $\sigma$ .

`samplepi0`, `samplepi1`, `subsample`: convenience functions for generating/loading samples corresponding to the prior and posterior distributions.

### **GynC - src/gc**

`Config`: base type storing configuration for the mcmc sampling (patient data, measurement error, initial proposal variance for mcmc, adaptivity of mcmc, thinning, initial values and priors)

`logprior(config, x)`, `logpost(config, x)`, `llh(config,x)`: log prior, posterior and likelihood values for sample `x`

`sample(config, iters)`: sample `iters` samples using the the AMM sampler from the Mamba.jl package

`batch([configs], [iters]; dir)`: sample the given configs in parallel on a cluster managed by ClusterManagers.jl and store them in the `dir` directory whenever any of the iterations in `[iters]` is reached.

`alldatas()`: load all present data

`gync(y0, p, t)`: compute a trajectory for given initial values, parameters and time using the Sundials CVode solver.