Identification of cell signaling pathways based on biochemical reaction kinetics repositories

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Introduction

Cell Signaling

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Understanding the functioning of cell signaling is important in many biological areas.

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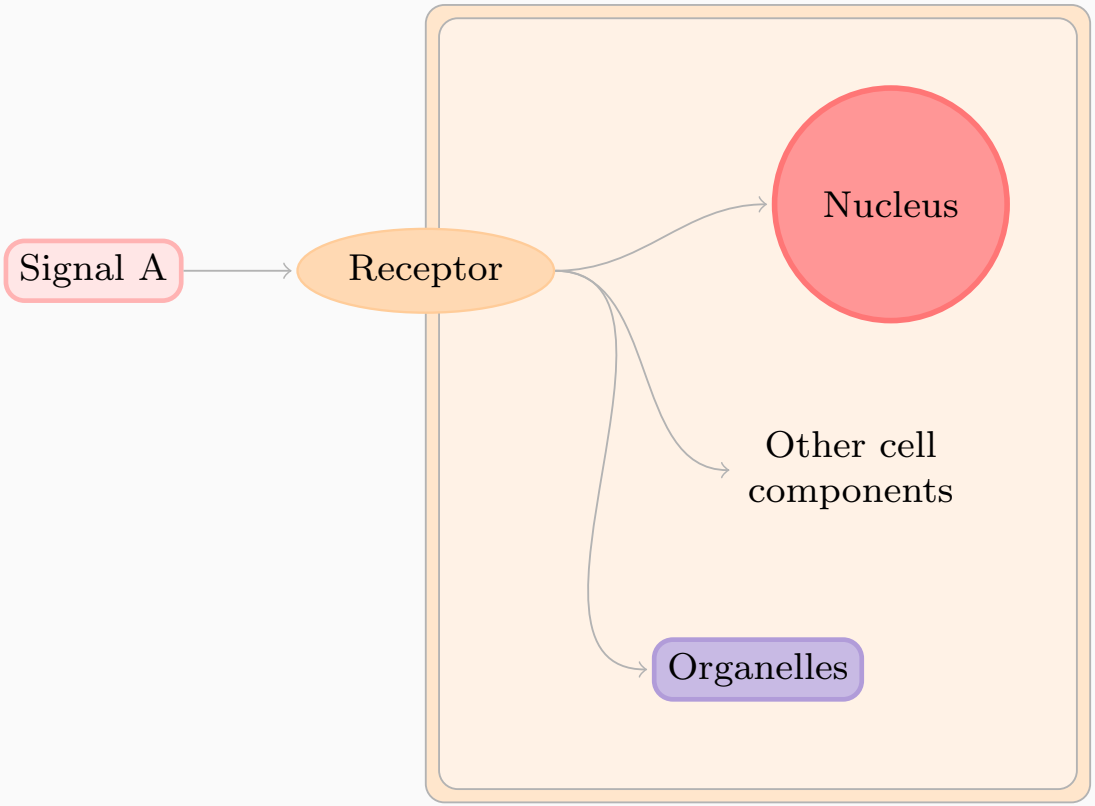

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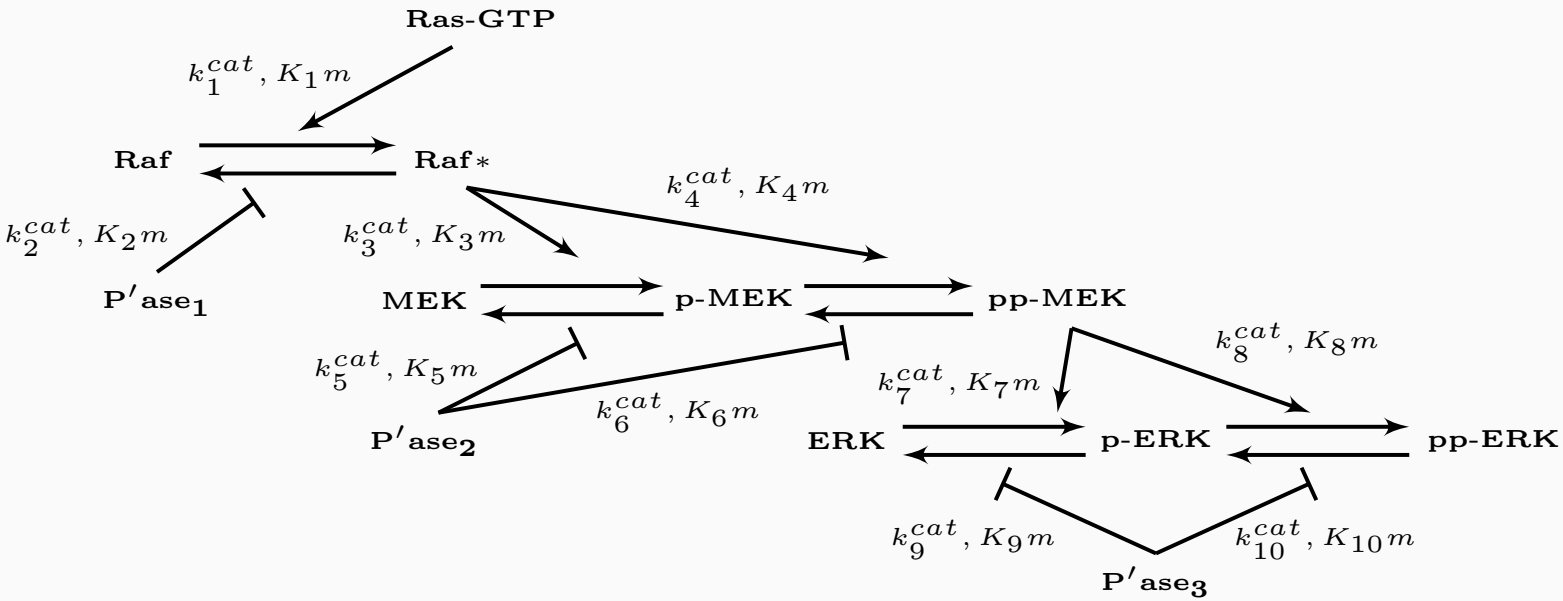
We call the path of a signal a cell signaling pathway.

Cell Signaling Pathways

A cell signaling network can be characterized by a sequence of chemical reactions



Mathematical Models of Signaling Networks

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Using biochemical and enzymatic kinetics, we can model the concentration change of chemical species over time of a pathway.

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- a model composed by a set of chemical reactions that are relevant for the biological experiment;
- information about the reaction rate constants of the model.

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One can search for the set of chemical reactions relevant for a biological experiment in repositories like the Kyoto Encyclopedia of Genes and Genomes (KEGG). However, the pathway maps from KEGG may be incomplete or have impertinent reactions for the biological experiment of interest.

Hence, it is desirable to construct a method that can systematically modify these models and choose the one that better represents the experiment.

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On her work, the problem of identification of cell signaling pathways is treated as a feature selection problem.

Feature Selection for Identification of Signaling Pathways

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Wu's Search Algorithm for Feature Selection

The search algorithm used by Wu is the Sequential Forward Selection (SFS).

Wu's Cost Function for Feature Selection

Wu defines the cost function as the minimum distance between experimental and simulated data.

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- the database of interactions used could be more nearly complete;
- the search algorithm could also consider removing interactions;
- the cost function could implement a proper penalization of models;

What we Propose on this Project

We propose to create a methodology that uses a feature selection approach for identification of signaling pathways, tackling the difficulty of penalizing complex models.

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We intend to use Bayesian approaches of model selection that allow us to create estimates of $p(M|D)$ or $p(D|M)$.

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- Implementation and comparison of cost functions for model selection.
- Formulate systematic modifications to a model as the search space of a feature selection model.
- Observe the surface induced by the cost function over the search space.

Fundamental Concepts

Kinetics Modeling of Chemical Reactions

Mathematical Modeling of Reactions

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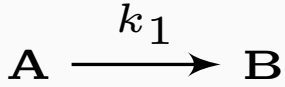
- first order interaction kinetics;
- second order interaction kinetics;
- Michaelis-Menten enzymatic kinetics.

Kinetic Modeling of First Order Iteration

A first order reaction:



Kinetic Modeling of First Order Iteration

A first order reaction:

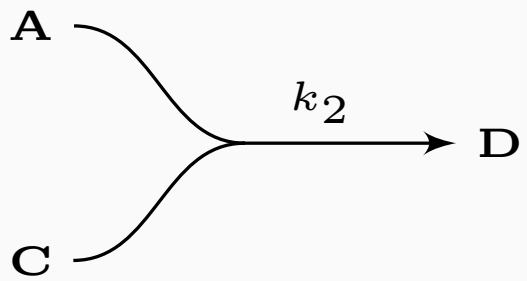
$$\mathbf{A} \xrightarrow{k_1} \mathbf{B}$$

has rate of:

$$k_1[\mathrm{A}].$$

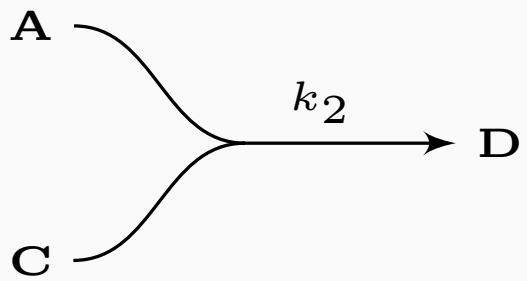
Kinetic Modeling of Second Order Iteration

A second order reaction:



Kinetic Modeling of Second Order Iteration

A second order reaction:

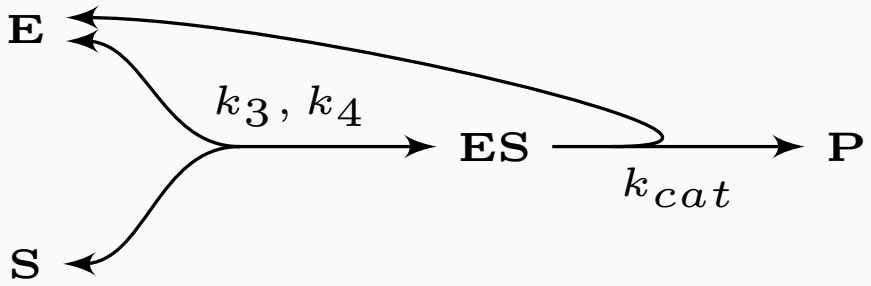


has rate of:

$$k_2[\mathrm{A}][\mathrm{C}].$$

Kinetic Modeling of Enzymatic Reactions

An enzymatic reaction:



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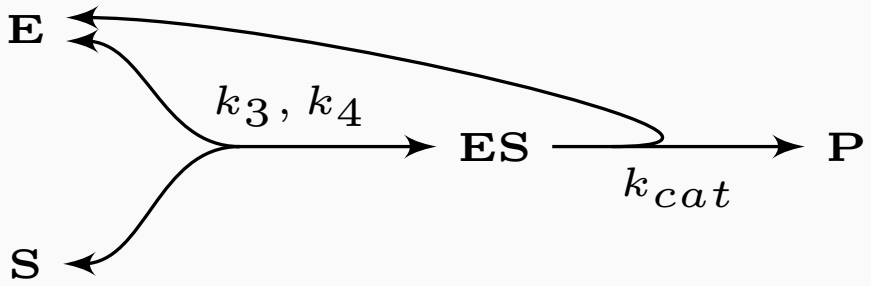

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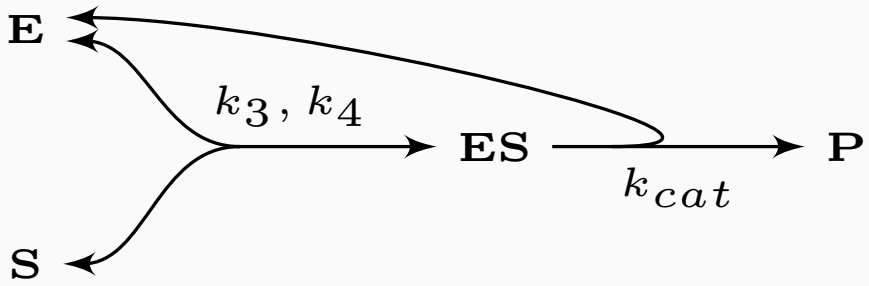
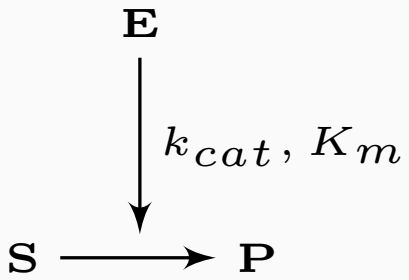


Can be divided in two first order reactions plus a second order reaction. However, with the appropriate assumptions, it is possible to use a Michaelis-Menten simplification of this reaction.

Michaelis-Menten Kinetics

We denote Michaelis-Menten simplification of the last enzymatic reaction as



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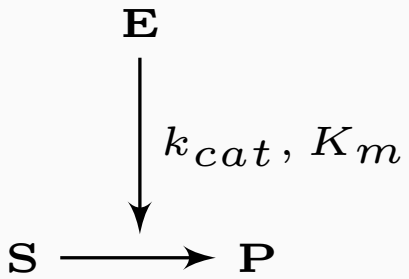
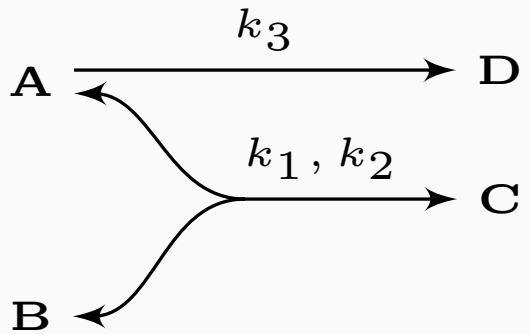


and it has rate of:

$$k_{cat} \frac{[\mathrm{E}][\mathrm{S}]}{K_M + [\mathrm{S}]}.$$

Kinetics of a System of Reactions

Suppose we want to model the kinetics of A on these reactions:



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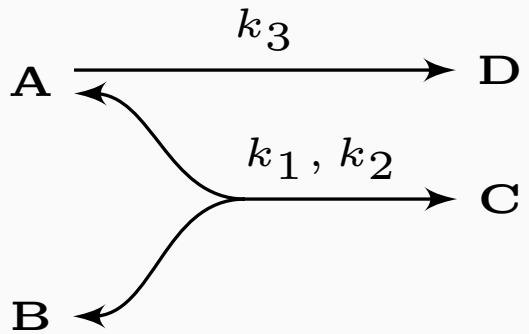

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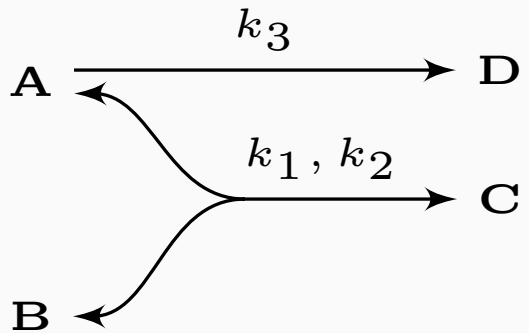

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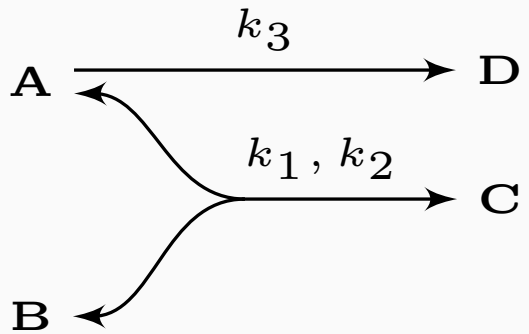

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- $C \longrightarrow A + B$, with rate $k_2[C]$,
- $A \longrightarrow D$, with rate $k_3[A]$.

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$$\frac{d[A]}{dt} = -k_1[A][B] + k_2[C] - k_3[D].$$

Bayesian Methods for Biochemical Model Selection

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For both methods, we resort to Metropolis-Hastings algorithm to generate samples of distributions.

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5. Increase t by one and repeat from Step 2 if not reached iteration limit.

Model Selection

Ranking with Marginal Likelihood Estimation

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If we consider that a model M with parameters θ correctly represent the signaling pathway and that there is a Gaussian observation error on D. Then, the likelihood of observing experimental data D is:

$$p(D|M,\theta) = p_{\mathcal{N}_{(\vec{0},\Sigma)}}(\phi(M,\theta) - D).$$

Where $\phi(M,\theta)$ is the simulated observation.

Marginal Likelihood of Data

We can marginalize the likelihood to obtain:

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Calculating this integral is hard, therefore we resort to estimating another integral.

Power-posterior distributions

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$$p_{\beta=1}(\theta) = \frac{p(D, \theta|M)}{\int_\Theta p(D, \theta|M) d\theta} = \frac{p(\theta|D, M)p(D|M)}{p(D|M)} = p(\theta|D, M).$$

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$$\ln p(D|M) = \int_0^1 \mathbb{E}_{p_\beta(\theta)}[\ln p(D|\theta, M)] d\beta.$$

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$$\sum_{t=0}^{T-1} (\beta_{t+1} - \beta_t) \frac{\mathbb{E}_{p_{\beta_{t+1}}(\theta)}[\log p(D|M,\theta)] + \mathbb{E}_{p_{\beta_t}(\theta)}[\log p(D|M,\theta)]}{2}$$

Estimating the Thermodynamic Integral

To produce the estimates of

$$\mathbb{E}_{p_{\beta_t}(\theta)}[\log p(D|M,\theta)] \text{ for } t \in \{0,\ldots,T\}$$

we need to produce samples of the power-posteriors $p_{\beta_t}(\theta)$.

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Sampling from the Power-posteriors

On the second sampling step, called posterior shaped burn-in, we use the covariance of the current sample times some constant as the covariance of the jump distribution.

Sampling from the Power-posteriors

On the third step, we perform the Populational Monte Carlo Markov Chain sampling. This algorithm allows us to mix samples from different power posteriors.

Ranking with Approximate Bayesian Computation

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4. Repeat until some iteration limit.

Approximate Bayesian Computation

The result of the algorithm is a sample of the distribution

$$p(\theta, M | d(\phi(M, \theta), D) < \epsilon).$$

ABC Sequential Monte Carlo

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We can use the accepted parameters of tolerance ϵ and model M to estimate

$$p(M|d(\phi(M,\theta)) < \epsilon).$$

Development of SigNetMS

The SigNetMS Software

A software that estimates the marginal likelihood

To choose a cost function, we needed to compare the ABC-SMC and Marginal Likelihood approaches for model selection.

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- `ABC-SysBio` is a software that implements `ABC-SMC`
- `BioBayes` is a software that implements the estimation of the marginal likelihood.

A software that estimates the marginal likelihood

However, the usage of `BioBayes` in our context was cumbersome.

A software that estimates the marginal likelihood

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Therefore, we decided to implement SigNetMS.

The SigNetMS software

SigNetMS is a Python package and command line software that estimates the marginal likelihood of a model given experimental data.

The input expected by SigNetMS

The input to SigNetMS includes:

- An SBML file model;
- An XML file with prior distributions of parameters;
- An XML file with experimental data;

The output produced by SigNetMS

SigNetMS produces an estimate of the marginal likelihood, as you may have suspected.

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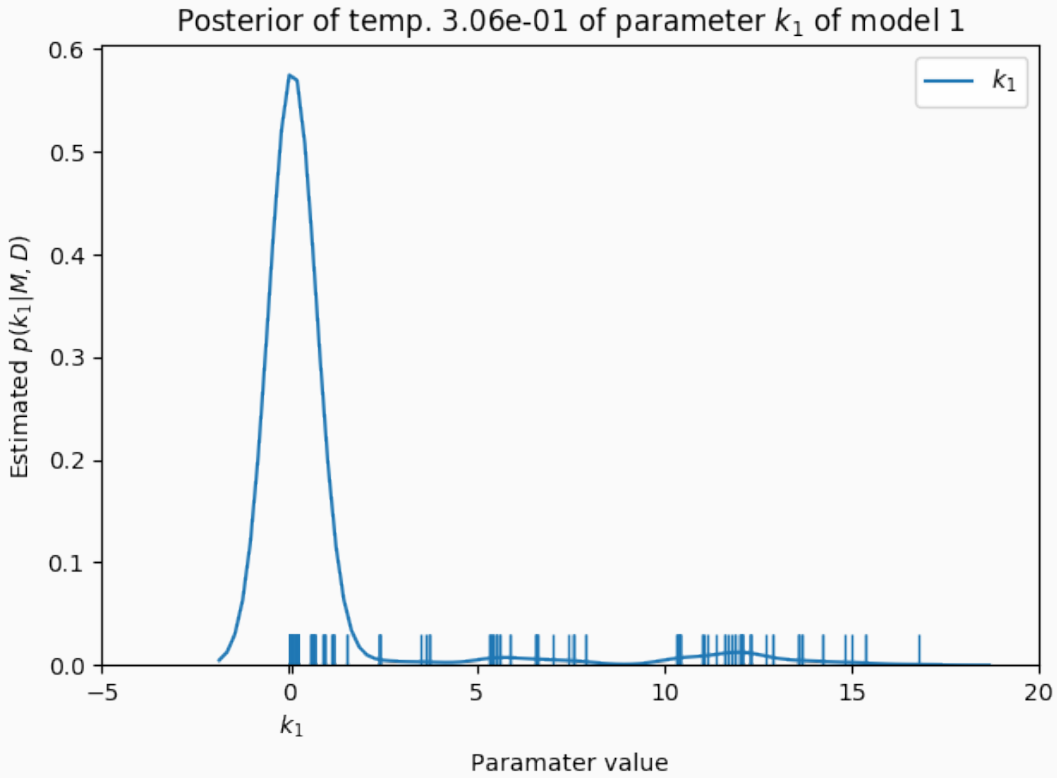

TODO: one class to fulfill credits requirements TODO: comment on focusing the database for our applications.

Thank you!