Tutorial 8

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Exercise: Profile likelihood

The profile likelihood method is used to assess confidence intervals of parameters in non-linear models. A model of the reaction flux of an enzymatic reaction associated with the substrate concentration [S] is given by

$$\dot{v} = \frac{10^{V_{max}} \cdot [S]}{10^{K_m} + [S]}. \tag{1}$$

Here, Km and Vmax denote the Michaelis-Menten constant and maximal flux on the log10 scale, respectively. Let us assume that the reaction flux $\dot{v}$ can be measured as a function of the substrate concentration and that the parameters V_{max} and K_m are to be determined from the experimental data.

- 1. Simulate the dose-response curve $\dot{v}([S])$ for parameters $K_m = 0$ and $V_{max} = 1$ and concentrations of [S] between 0 and 2. Plot the result.
- 2. For concentrations [S]$\in \{.1, .5, 1, 2\}$ simulate the model prediction and pick normally distributed random numbers around the prediction with a standard deviation of 7%. These values represent the simulated data with measurement uncertainty. Add the data points with error bars to the previous plot.
- 3. The basis of the profile-likelihood method is the log-likelihood function and a maximum-likelihood fit serving as the point of departure for the profile likelihood analysis. Define the negative log-likelihood as a `function L(conc, flux, std, p)` of the substrate concentration *conc*, the $flux$ and *std* (simulated in 2) and the parameters $p = \{K_m, V_{max}\}$. Then, use `optimum = optimize(p -> L(conc, flux, std, p), init, Newton())` from the `Optim` package to minimize the negative log-likelihood and obtain parameter estimates.
- 4. Now, implement a function `function L1(conc, flux, std, pfix, whichPar, p)` which calculates the likelihood for one fixed parameter $pfix$, $whichPar = \{1, 2\}$ the parameter which you intend to fit and p the parameter to be fitted.

- 5. Implement a function profile(optimum, L1, whichPar) for the profile-likelihood method. In principle, the algorithm should include:
  a while-loop to compute the deviance between the original LL-value and the new LL-value after refitting for the stepwise increased parameter value.
  a for-loop to include both directions (sig) for the profile computation starting from the optimum.
  The algorithm should have the general form:

  ```
  Initialize arrays
  For sig in (-1, 1)
      Set deviance to 0
      While deviance < 4 and parameter values in [-5, 5]
          Set the fixed parameter step by step: value[whichPar] + sig*step
          fit the model
          compute deviance = ( logLik(fit_0) - logLik(fit_new) )
          Save deviance, fixed parameter and fitted parameters for every step
      end
      return dev, pfit, pfix
  end
  ```

  and should return the deviance (the difference of twice the negative log-likelihood between the refit and the original fit), fixed (the value of the parameter held fixed during max-likelihood estimation) and fitted parameters (the fit result per iteration of the while-loop). Show the results in a plot showing the fixed parameter value vs. the deviance and secondly a plot showing K_m vs V_{max} for each of the profiles.

- 6. For the above choice of substrate concentrations we find that the profiles of both parameters exceed the deviance threshold associated with a 95% confidence level. Repeat steps 1-4 for simulated data points with $[S] \in (0, .1]$ or with $[S] \in [5, 10]$. Interpret the results obtained for the likelihood-profiles and profile paths.

Cathedral exercise

How does the cathedral relate to the symposium of Plato? Study the Apocalypse of Saint John and the writings of Proklos, Plotinus and the Abbot Suger of St. Denis.