**Notes**

(1) Difference to ECM: here,usually do not fix any of the metabolite concentrations (but use ranges and distributions for all of them) (may also be better in ECM for numerics ..). However, in the example case shown (just for didactical purposes), we assume that the external concentrations S and P are fixed and that only the concentration of A (or $x = \ln c_{\mathrm{A}}$) can be varied.

(2) Here we consider only a variable $x$ , the kinetic constants remain the same. However, the general problem of convexity (or non-convexity) remains the same if we consider log concentrations and log kinetic constants as our variables.

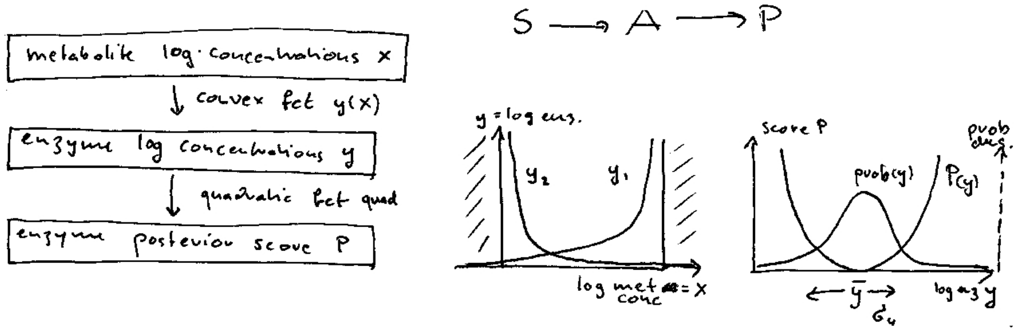
(3) In the plots for the 1-dim case, the column on the right shows a case in which the data for enzyme levels are correct, so there is no discrepancy between them. In this case, the score function is more likely (but still not guaranteed) to be convex even without the "rest" term. The most problematic case (strongly not-convex functions) occurs when enzyme data point do not coincide with the true value, but are much larger and (wrongly) very small measurement errors are assumed.

(4) in the column on the left, there can be local minima that correspond to a better fit of enzyme 2 or a better fit of enzyme 1, respectively.

(5) To obtain convex functions, we could, in theory, assume very broad enzyme measurement uncertainties. This, basically corresponds to downscaling the enzyme term in comaprison to the rest term, and at some point, the rest term would dominta and make the total score convex. However, what we're doing with alpha is basically this, we're just doing it selectively for parts of the score functions that are potentially problematic for convexity. There is no need to downscale the other parts.

(6) To prove convexity, we consider (i) the "variable" part of the enzyme score, which scales with alpha and is non-convex (ii) the non-variable part plus the rest term, which is constant and strictly convex. Both functions (let us call them $f(\mathbf{x})$ and $g(\mathbf{x})$) are smooth and differentiable on the polytope, with Hessian matrices $H_f(\mathbf{x})$ and $H_g(\mathbf{x})$. If $g$ is strictly convex, then $H_g(\mathbf{x})$ is strictly positive everywhere on the polytyope, and there exists an $\alpha > 0$ such that also $\alpha\, H_f(\mathbf{x}) + H_g(\mathbf{x})$ is strictly positive everywhere on the polytyope.

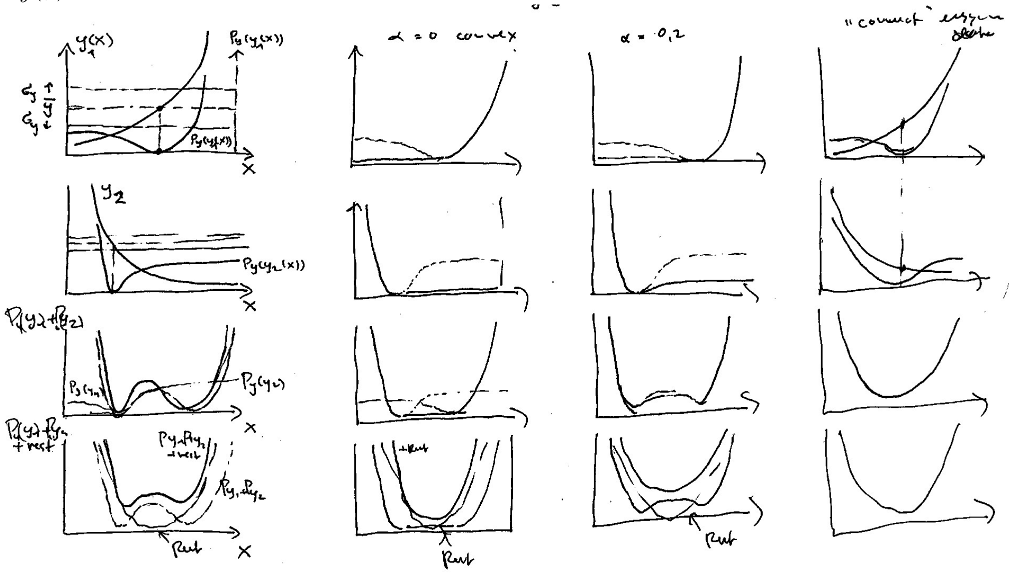
Functions




$$\text{Score } P = -\ln \text{Prob}(y) \sim \frac{(y-\bar{y})^2}{2\sigma_y^2} \quad \text{or} \quad \frac{1}{2}(y-\bar{y})^T \Sigma_y^{-1} (y-\bar{y})$$

1-dimensional case

Problem: enzyme score $P_y(y(x))$ is not convex in x! Trick: omit or scale down left half of the quadratic function $P_y(y)$




2-dimensional case

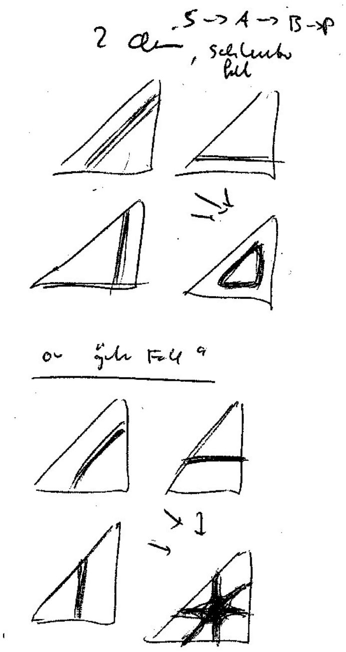
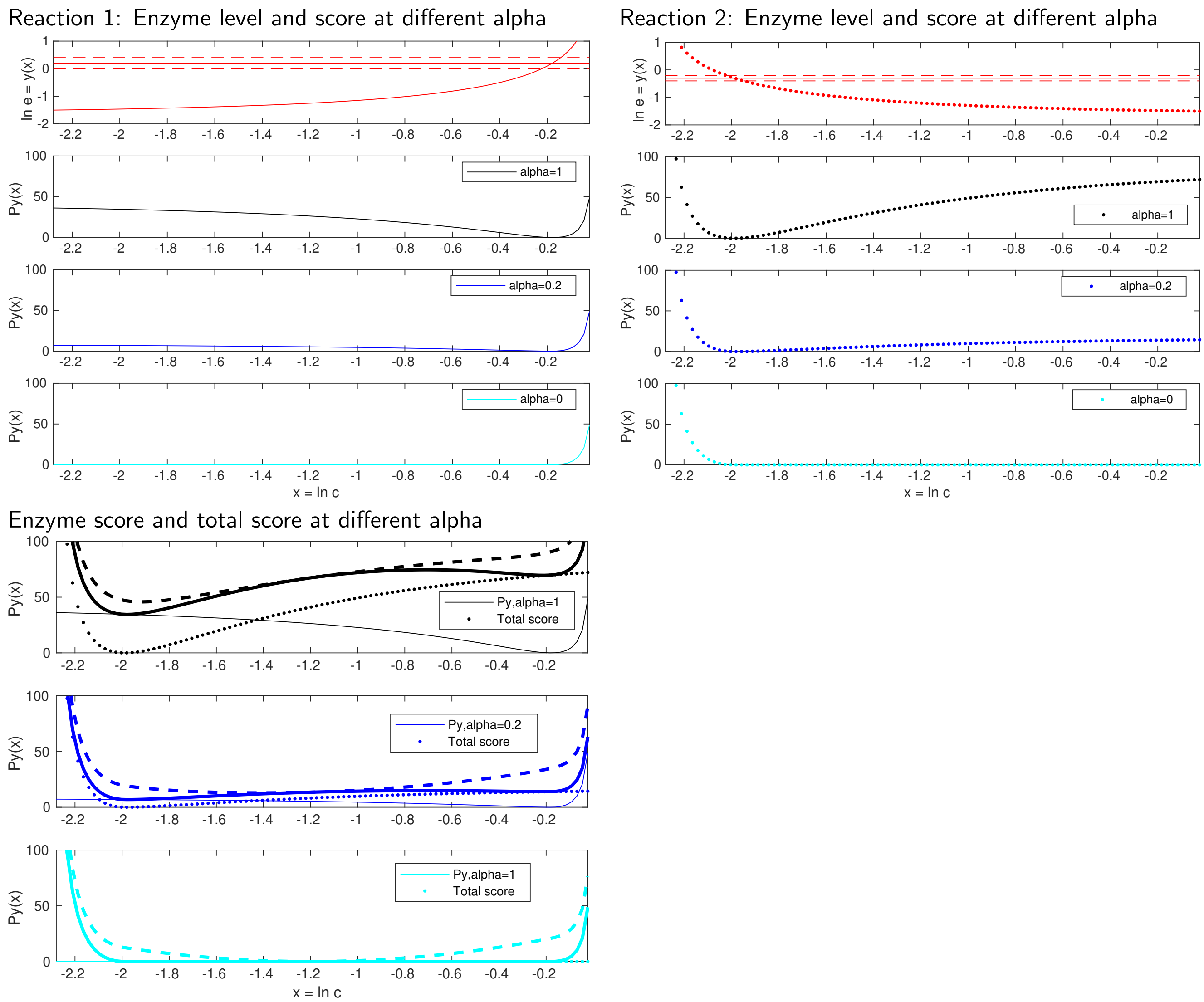



Figure 1:



Reaction 1: Enzyme level and score at different alpha
Reaction 2: Enzyme level and score at different alpha
ln e = y(x)
Py(x)
alpha=1
alpha=0.2
alpha=0
x = ln c
Enzyme score and total score at different alpha
Py,alpha=1
Total score
Py,alpha=0.2
Total score
Py,alpha=1
Total score


Figure 2: