Computing Parametric Images from Dynamic Sequences Using A QR Decomposition Method

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I. Introduction

Despite the continuing remarkable increase of computing speed, the belief persists that nonlinear pixel-by-pixel kinetic images are impractical for routine use. This paper presents an efficient method for computing parametric images. The key feature of the method is that we minimize computation per pixel by precomputing tables of QR factorizations. We also describe an efficient algorithm for enforcing nonnegativity of the natural kinetic parameters.

For 40 planes of 64 by 64 images of 26 frames, only ? seconds are required for ?

We focus on the two-compartment model, although the general approach applies to more complicated models.

Table search also performed by [1]

II. Model

Let $c_1(t)$ and $c_2(t)$ represent the radioisotope concentrations in compartments 1 and 2 of Fig. 1 respectively, and let $c_p(t)$ denote the plasma concentration (input function). Then the governing differential equation is

$$\dot{\boldsymbol{c}}(t) = -\boldsymbol{A}\boldsymbol{c}(t) + K_1 \begin{bmatrix} 1 \\ 0 \end{bmatrix} c_p(t),$$

where

$$\boldsymbol{c}(t) = \begin{bmatrix} c_1(t) \\ c_2(t) \end{bmatrix}, \text{ and } \boldsymbol{A} = \begin{bmatrix} k_2 + k_3 & -k_4 \\ -k_3 & k_4 \end{bmatrix}.$$

Given this differential equation, we first want to obtain an expression for the total tissue concentration:

$$c(t) = c_1(t) + c_2(t).$$

We do this by diagonalizing the differential equation.

The eigenvalues of $\boldsymbol{A}$ can be found by setting $|\boldsymbol{A} - \lambda \boldsymbol{I}| = 0$, yielding:

$$\lambda^{\pm} = \frac{1}{2}(k_2 + k_3 + k_4) \pm \frac{1}{2}\sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}.$$

Note that if $k_4 = 0$, then

$$\lambda^{\pm} = \{(k_2 + k_3),\ 0\}.$$

Eigenvectors of $\boldsymbol{A}$ are found by setting $(\boldsymbol{A} - \lambda^{\pm}\boldsymbol{I})\boldsymbol{v}^{\pm} = 0$, yielding (for example):

$$\boldsymbol{v}^{\pm} = \begin{bmatrix} k_4 - \lambda^{\pm} \\ k_3 \end{bmatrix}.$$

Let $\boldsymbol{V} = [\boldsymbol{v}^{+}\ \boldsymbol{v}^{-}]$, then

$$\boldsymbol{A}\boldsymbol{V} = \boldsymbol{V}\boldsymbol{\Lambda}, \text{ where } \boldsymbol{\Lambda} = \begin{bmatrix} \lambda^{+} & 0 \\ 0 & \lambda^{-} \end{bmatrix}.$$

Thus $\boldsymbol{A} = \boldsymbol{V}\boldsymbol{\Lambda}\boldsymbol{V}^{-1}$, so

$$\dot{\boldsymbol{c}}(t) = -\boldsymbol{V}\boldsymbol{\Lambda}\boldsymbol{V}^{-1}\boldsymbol{c}(t) + K_1 \begin{bmatrix} 1 \\ 0 \end{bmatrix} c_p(t)$$

or

$$\boldsymbol{V}^{-1}\dot{\boldsymbol{c}}(t) = -\boldsymbol{\Lambda}\boldsymbol{V}^{-1}\boldsymbol{c}(t) + K_1\boldsymbol{V}^{-1} \begin{bmatrix} 1 \\ 0 \end{bmatrix} c_p(t).$$

Define $\boldsymbol{w}(t) = \boldsymbol{V}^{-1}\boldsymbol{c}(t)$, then

$$\dot{\boldsymbol{w}}(t) = -\boldsymbol{\Lambda}\boldsymbol{w}(t) + K_1\boldsymbol{V}^{-1} \begin{bmatrix} 1 \\ 0 \end{bmatrix} c_p(t). \tag{1}$$

One can compute $\boldsymbol{V}^{-1}$ to show that

$$\boldsymbol{V}^{-1} \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \frac{1}{\lambda^{+} - \lambda^{-}} \begin{bmatrix} -1 \\ 1 \end{bmatrix}.$$

Since $\boldsymbol{\Lambda}$ is diagonal, (1) is a separable differential equation, whose solution is:

$$\boldsymbol{w}(t) = \frac{K_1}{\lambda^{+} - \lambda^{-}} \begin{bmatrix} -e^{-t\lambda^{+}} \\ e^{-t\lambda^{-}} \end{bmatrix} \otimes c_p(t),$$

where $\otimes$ denotes convolution.

Noting that

$$c(t) = [1\ 1]\ \boldsymbol{c}(t) = [1\ 1]\ \boldsymbol{V}w(t),$$

we can substitute back to show that

$$c(t) = \frac{K_1}{\lambda^{+} - \lambda^{-}}[(\lambda^{+} - k_3 - k_4)e^{-t\lambda^{+}} + (k_3 + k_4 - \lambda^{-})e^{-t\lambda^{-}}] \otimes c_p(t).$$

In particular, if $k_4 = 0$, then

$$c(t) = K_1 \left[\frac{k_2}{k_2 + k_3}e^{-(k_2+k_3)t} + \frac{k_3}{k_2 + k_3}e^{-0t}\right] \otimes c_p(t).$$

We measure the average tissue concentration $c(t)$ over n time intervals $[t_i^L, t_i^R], i = 1, \ldots, n$. In addition there is a contribution due to blood activity $b(t)$. So the (noiseless) measured counts are proportional to:

$$y_i = \frac{1}{t_i^R - t_i^L} \int_{t_i^L}^{t_i^R} 2^{-(t-t_0)/T_h}[(1-\beta)c(t) + \beta b(t)]\, dt, \tag{2}$$

where T_h is the half-life of the radio-isotope, t_0 is a reference time, and the $2^{-(t-t_0)/T_h}$ factor represents the decay of radioactivity. Assuming the time intervals are small enough relative to the tissue kinetics, one can bring the decay factor outside of the integral and precorrect the measurements y_i. In the remainder of this paper we assume the y_i's have been precorrected for radioisotope decay, so we disregard the $2^{-(t-t_0)/T_h}$ factor.

Define

$$\begin{aligned} s_{0,i} &= \frac{1}{t_i^R - t_i^L} \int_{t_i^L}^{t_i^R} b(t)\, dt, \\ s_{1,i}(\lambda) &= \frac{1}{t_i^R - t_i^L} \int_{t_i^L}^{t_i^R} e^{-\lambda t} \otimes c_p(t)\, dt. \end{aligned} \tag{3}$$

Then we can rewrite (2) as

$$y_i = (1-\beta)\frac{K_1}{\lambda^+ - \lambda^-}\left[(\lambda^+ - k_3 - k_4)\cdot s_{1,i}(\lambda^+) + (k_3 + k_4 - \lambda^-)\cdot s_{1,i}(\lambda^-)\right] + \beta \cdot s_{0,i}. \tag{4}$$

Now define[1]

$$\begin{aligned} \theta_0 &= \beta \\ \theta_1 &= (1-\beta)K_1(\lambda^+ - k_3 - k_4)/(\lambda^+ - \lambda^-) \\ \theta_2 &= (1-\beta)K_1(k_3 + k_4 - \lambda^-)/(\lambda^+ - \lambda^-) \\ \underline{\lambda} &= [\lambda^+\ \lambda^-], \end{aligned} \tag{5}$$

and stack everything into vectors:

$$\boldsymbol{y} = \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix}, \quad \boldsymbol{s}_j = \begin{bmatrix} s_{j,1} \\ \vdots \\ s_{j,n} \end{bmatrix}, \quad j = 0, 1,$$

and define

$$\boldsymbol{S}_{\underline{\lambda}} = [\boldsymbol{s}_0\ \boldsymbol{s}_1(\lambda^+)\ \boldsymbol{s}_1(\lambda^-)]. \tag{6}$$

Then we can rewrite (4):

$$\boldsymbol{y} = \boldsymbol{S}_{\underline{\lambda}}\, \boldsymbol{\theta}, \tag{7}$$

where $\boldsymbol{\theta} = [\theta_0\ \theta_1\ \theta_2]'$.

After estimating $\underline{\lambda}$ and $\boldsymbol{\theta}$, we can convert back to the kinetic parameters by inverting (5). In particular, if $k_4 = 0$ (i.e., λ^- is fixed to 0), then

$$\begin{aligned} \beta &= \theta_0 \\ K_1 &= (\theta_1 + \theta_2)/(1 - \theta_0). \\ k_2 &= \lambda^+\theta_1/(\theta_1 + \theta_2) \\ k_3 &= \lambda^+\theta_2/(\theta_1 + \theta_2) \end{aligned}$$

For fitting with $k_4 \neq 0$, the formulae are:

$$\begin{aligned} \beta &= \theta_0 \\ K_1 &= (\theta_1 + \theta_2)/(1 - \theta_0) \\ k_2 &= (\lambda^+\theta_1 + \lambda^-\theta_2)/(\theta_1 + \theta_2) \\ k_4 &= \lambda^+\lambda^-/k_2 \\ k_3 &= (\lambda^+\theta_2 + \lambda^-\theta_1)/(\theta_1 + \theta_2) - k_4. \end{aligned} \tag{8}$$

[1] One can verify that since the kinetic parameters are positive and $\beta \in [0, 1)$, then $\lambda^+ > \lambda^-$, and θ_1 and θ_2 are positive.

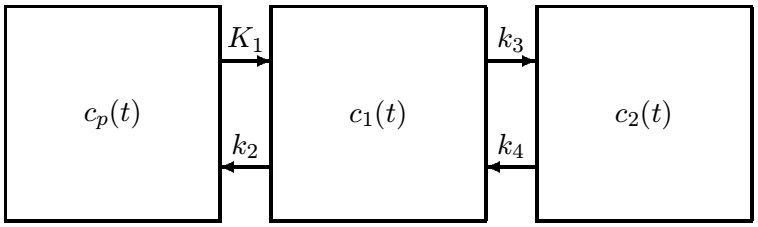

Fig. 1. Two compartment model.

III. Estimation

The above description focussed on a two-compartment model, but the form of the final equation (7) is applicable to any time-invariant linear differential equation, i.e., we can generally write:

$$\boldsymbol{y} = \boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta} + \text{ noise.}$$

For (unweighted) kinetic fitting, we would like to minimize

$$\|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta}\|^2$$

over $\boldsymbol{\theta}$ and $\underline{\lambda}$, subject to the constraint that $\boldsymbol{\theta} \geq 0$. We first consider the unconstrained case. The utility of the form (7) is that we have transformed the estimation problem so that the nonlinear and linear components are separated. The idea behind the QR approach is to use a brute-force table search for minimization over $\underline{\lambda}$ and to use the analytical minimization over $\boldsymbol{\theta}$ since that part is linear. In other words, we write the minimization as two parts:

$$\min_{\underline{\lambda}} \min_{\boldsymbol{\theta}} \|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta}\|^2.$$

For the inner minimization over $\boldsymbol{\theta}$, we think of $\underline{\lambda}$ as being fixed. It is easily shown that the least-squares estimate for $\boldsymbol{\theta}$ is

$$\hat{\boldsymbol{\theta}}_{\underline{\lambda}} = [\boldsymbol{S}'_{\underline{\lambda}}\boldsymbol{S}_{\underline{\lambda}}]^{-1}\boldsymbol{S}'_{\underline{\lambda}}\boldsymbol{y} = [\boldsymbol{R}'_{\underline{\lambda}}\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{R}_{\underline{\lambda}}]^{-1}\boldsymbol{R}'_{\underline{\lambda}}\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y} = \boldsymbol{R}_{\underline{\lambda}}^{-1}\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y},$$

where $'$ denotes matrix transposition, and $\boldsymbol{S}_{\underline{\lambda}} = \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{R}_{\underline{\lambda}}$ is the QR decomposition of $\boldsymbol{S}_{\underline{\lambda}}$ [2], where $\boldsymbol{Q}_{\underline{\lambda}}$ is a $n \times 3$ matrix whose columns are orthonormal, and $\boldsymbol{R}_{\underline{\lambda}}$ is an upper-triangular invertible 3×3 matrix. (The QR decomposition can be formed using the Gram-Schmidt procedure.) The key to the efficiency of our approach is the for a set (i.e. table) of values $\underline{\lambda} \in \Gamma$, we compute $\boldsymbol{S}_{\underline{\lambda}}$ using (3) and (6), and then precompute $\boldsymbol{Q}_{\underline{\lambda}}$ and $\boldsymbol{R}_{\underline{\lambda}}$. Thus

$$\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\hat{\boldsymbol{\theta}}_{\underline{\lambda}} = \boldsymbol{y} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{R}_{\underline{\lambda}}\boldsymbol{R}_{\underline{\lambda}}^{-1}\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y} = (\boldsymbol{I} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{Q}'_{\underline{\lambda}})\boldsymbol{y}.$$

Therefore,

$$\|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\hat{\boldsymbol{\theta}}_{\underline{\lambda}}\|^2 = \|(\boldsymbol{I} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{Q}'_{\underline{\lambda}})\boldsymbol{y}\|^2 = \|\boldsymbol{y}\|^2 - \|\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y}\|^2.$$

Thus the outer minimization becomes

$$\min_{\underline{\lambda}\in\Gamma} \left(\|\boldsymbol{y}\|^2 - \|\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y}\|^2\right) = \max_{\underline{\lambda}\in\Gamma} \|\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y}\|^2.$$

The algorithm works as follows. In Matlab, we use `kinetic1_mex()` to compute $\boldsymbol{S}_{\underline{\lambda}}$ using (3) and (6) for each $\underline{\lambda} \in \Gamma$, and then we precompute $\boldsymbol{Q}_{\underline{\lambda}}$ and $\boldsymbol{R}_{\underline{\lambda}}^{-1}$. In the C program, for each value of $\underline{\lambda} \in \Gamma$, we compute $\|\boldsymbol{Q}'_{\underline{\lambda}}\boldsymbol{y}\|^2$, which is simply 3 inner products and a sum. Let $\hat{\underline{\lambda}}$ be the value that gives the largest norm. This value is found using a table search whose dimension is the number of unconstrained components of $\underline{\lambda}$. We then form:

$$\hat{\boldsymbol{\theta}} = \boldsymbol{R}_{\hat{\underline{\lambda}}}^{-1}\, \boldsymbol{Q}'_{\hat{\underline{\lambda}}}\boldsymbol{y}.$$

Note that by precomputing the inverse $\boldsymbol{R}_{\underline{\lambda}}^{-1}$ in Matlab, no matrix inversions are required in the C program. This simplifies the C program. Now that we have estimates for $\underline{\lambda}$ and $\boldsymbol{\theta}$, we can solve back for the kinetic parameters using (8).

IV. Nonnegativity Constraint

The method as described above does not enforce nonnegativity. In some sense this may be desirable since negative values serve as a warning to the user that the data needs to be inspected more closely. However, since negative values for $\boldsymbol{\theta}$ are not physically meaningful, in some applications it would desirable to use a method that explicitly enforces the nonnegativity constraint *during estimation* rather than simply clipping the negative values to zero after the fact. This section describes one approach for constrained minimization that again makes use of precomputed tables. For generality, we initially consider arbitrary equality constraints.

Consider the m constraints $(\boldsymbol{c}_1'\boldsymbol{\theta} = b_1),\ \ldots,\ (\boldsymbol{c}_m'\boldsymbol{\theta} = b_m)$ or

$$\boldsymbol{C}'\boldsymbol{\theta} = \boldsymbol{b},\ \ \boldsymbol{C} = [\boldsymbol{c}_1\ \ldots\ \boldsymbol{c}_m].$$

Applying the method of Lagrange to minimize $\|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta}\|^2$, we would like to first minimize over $\boldsymbol{\theta}$

$$\frac{1}{2}\|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta}\|^2 + \sum_{k=1}^{m} \gamma_k(\boldsymbol{c}_k'\boldsymbol{\theta} - b_m).$$

Setting the gradient to zero:

$$\boldsymbol{0} = -\boldsymbol{S}_{\underline{\lambda}}'\boldsymbol{y} + \boldsymbol{S}_{\underline{\lambda}}'\boldsymbol{S}_{\underline{\lambda}}\boldsymbol{\theta} + \boldsymbol{C}\boldsymbol{\gamma},\ \ \boldsymbol{\gamma} = [\gamma_1\ \ldots\ \gamma_m]'.$$

Thus since $\boldsymbol{S}_{\underline{\lambda}} = \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{R}_{\underline{\lambda}}$:

$$\hat{\boldsymbol{\theta}} = (\boldsymbol{S}_{\underline{\lambda}}'\boldsymbol{S}_{\underline{\lambda}})^{-1}(\boldsymbol{S}_{\underline{\lambda}}'\boldsymbol{y} - \boldsymbol{C}\boldsymbol{\gamma}) = (\boldsymbol{R}_{\underline{\lambda}}'\boldsymbol{R}_{\underline{\lambda}})^{-1}(\boldsymbol{R}_{\underline{\lambda}}'\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{y} - \boldsymbol{C}\boldsymbol{\gamma}) = \boldsymbol{R}_{\underline{\lambda}}^{-1}(\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{y} - \boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}),$$

where $\boldsymbol{M}_{\underline{\lambda}} = (\boldsymbol{R}_{\underline{\lambda}}')^{-1}\boldsymbol{C}$, and

$$\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\hat{\boldsymbol{\theta}} = (\boldsymbol{I} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{Q}_{\underline{\lambda}}')\boldsymbol{y} + \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}.$$

Thus

$$\begin{aligned}\|\boldsymbol{y} - \boldsymbol{S}_{\underline{\lambda}}\hat{\boldsymbol{\theta}}\|^2 &= \|(\boldsymbol{I} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{Q}_{\underline{\lambda}}')\boldsymbol{y}\|^2 + 2\langle \boldsymbol{y}'(\boldsymbol{I} - \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{Q}_{\underline{\lambda}}'), \boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}\rangle + \|\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}\|^2 \\ &= \|\boldsymbol{y}\|^2 - \|\boldsymbol{Q}_{\underline{\lambda}}'\boldsymbol{y}\|^2 + \|\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}\|^2.\end{aligned}$$

Thus the minimization over $\underline{\lambda}$ is equivalent to maximizing

$$\|\boldsymbol{Q}_{\underline{\lambda}}'\boldsymbol{y}\|^2 - \|\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}\|^2.$$

Solving for $\boldsymbol{\gamma}$:

$$\boldsymbol{b} = \boldsymbol{C}'\hat{\boldsymbol{\theta}} = \boldsymbol{C}'\boldsymbol{R}_{\underline{\lambda}}^{-1}(\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{y} - \boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}), = \boldsymbol{M}_{\underline{\lambda}}'(\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{y} - \boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}),$$

thus

$$\boldsymbol{\gamma} = (\boldsymbol{M}_{\underline{\lambda}}'\boldsymbol{M}_{\underline{\lambda}})^{-1}(\boldsymbol{M}_{\underline{\lambda}}'\boldsymbol{Q}_{\underline{\lambda}}\boldsymbol{y} - \boldsymbol{b}).$$

Define $\boldsymbol{z}_{\underline{\lambda}} = \boldsymbol{Q}_{\underline{\lambda}}'\boldsymbol{y}$ and let the QR decomposition of $\boldsymbol{M}_{\underline{\lambda}}$ be $\boldsymbol{M}_{\underline{\lambda}} = \boldsymbol{P}_{\underline{\lambda}}\boldsymbol{U}_{\underline{\lambda}}$, then

$$\boldsymbol{\gamma} = (\boldsymbol{U}_{\underline{\lambda}}'\boldsymbol{U}_{\underline{\lambda}})^{-1}(\boldsymbol{U}_{\underline{\lambda}}'\boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{z}_{\underline{\lambda}} - \boldsymbol{b}) = \boldsymbol{U}_{\underline{\lambda}}^{-1}(\boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{z}_{\underline{\lambda}} - (\boldsymbol{U}_{\underline{\lambda}}')^{-1}\boldsymbol{b}).$$

Thus

$$\|\boldsymbol{M}_{\underline{\lambda}}\boldsymbol{\gamma}\|^2 = \|\boldsymbol{P}_{\underline{\lambda}}(\boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{z}_{\underline{\lambda}} - (\boldsymbol{U}_{\underline{\lambda}}')^{-1}\boldsymbol{b})\|^2 = \|\boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{z}_{\underline{\lambda}} - (\boldsymbol{U}_{\underline{\lambda}}')^{-1}\boldsymbol{b}\|^2$$

and

$$\hat{\boldsymbol{\theta}}_{\underline{\lambda}} = \boldsymbol{R}_{\underline{\lambda}}^{-1}[(\boldsymbol{I} - \boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{P}_{\underline{\lambda}})\boldsymbol{Q}_{\underline{\lambda}}'\boldsymbol{y} + \boldsymbol{P}_{\underline{\lambda}}(\boldsymbol{U}_{\underline{\lambda}}')^{-1}\boldsymbol{b}].$$

For nonnegativity constraint, we have $\boldsymbol{b} = \boldsymbol{0}$ and the following constraint matrices:

$$\boldsymbol{e}_1,\ \boldsymbol{e}_2,\ \boldsymbol{e}_3,\ [\boldsymbol{e}_2\ \boldsymbol{e}_3],\ [\boldsymbol{e}_1\ \boldsymbol{e}_3],\ [\boldsymbol{e}_1\ \boldsymbol{e}_2],$$

where $\boldsymbol{e}_j$ is the jth standard unit vector of length 3.

To initialize the algorithm ... ?

The algorithm is to tabulate ... ?

Thus

$$\max_{\underline{\lambda}}\ \left(\|\boldsymbol{z}_{\underline{\lambda}}\|^2 - \|\boldsymbol{P}_{\underline{\lambda}}'\boldsymbol{z}_{\underline{\lambda}}\|^2\right)$$

V. Nonlinear Constraints

One would like to be able to impose constraints on the original kinetic parameters, such as fixing k_4 to a specified value, or fixing the ratio K_1/k_2.

???????????? How to do this ??????????????

VI. Acknowledgement

Many thanks to Ray Raylman for his careful reading.

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