Metabolic Modelling

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1. Basic Linear Algebra (Based partly on the material of the course Linear Algebra Methods for Data Mining by Saara Hyvönen)

Matrices

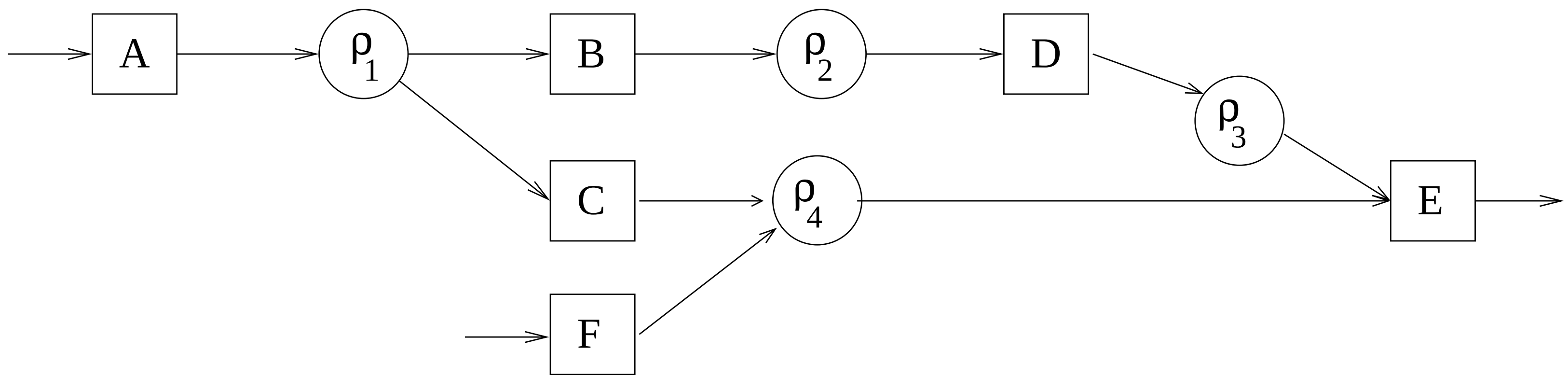
$$\mathbf{A} = \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & & \vdots \\ a_{m1} & a_{m2} & \cdots & a_{mn} \end{pmatrix} \in \mathbb{R}^{m \times n}$$

Rectangular array of data: elements are real numbers.

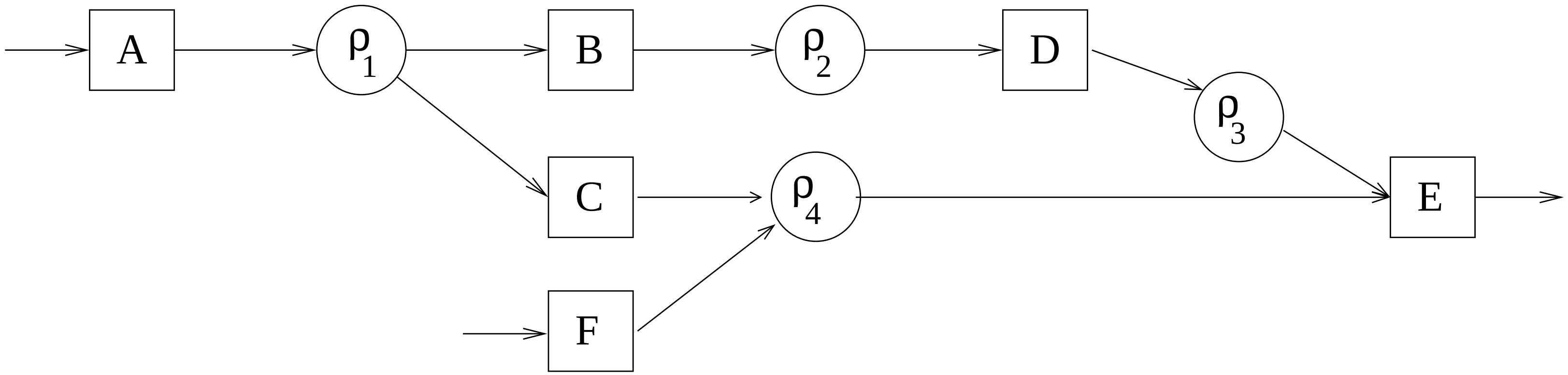
Metabolic networks

- Metabolic networks can be modelled as bipartite graphs
  - Reactions ρ_i transform substrate metabolites to product metabolites

$$\rho_1 : \mathrm{A} \rightarrow \mathrm{B} + \mathrm{C} \quad \rho_2 : \mathrm{B} \rightarrow \mathrm{D} \quad \rho_3 : \mathrm{D} \rightarrow \mathrm{E} \quad \rho_4 : \mathrm{C} + \mathrm{F} \rightarrow \mathrm{E}$$



Metabolic networks as matrices



$$\begin{array}{r} A: \\ B: \\ C: \\ D: \\ E: \\ F: \end{array}\begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 1 & 0 & 0 & -1 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & -1 \end{bmatrix} * \begin{bmatrix} v1 \\ v2 \\ v3 \\ v4 \end{bmatrix} = \begin{bmatrix} -v1 \\ 0 \\ 0 \\ 0 \\ v3+v4 \\ -v4 \end{bmatrix}$$

By studying the properties of the stoichiometric matrix with linear algebra we get information about the corresponding metabolic network!

Basic matrix operations

- Transpose $\mathbf{A}^T$ of $\mathbf{A}$: Interchange rows and columns.
  - $\mathbf{A}^T = [a_{ik}]^T = [a_{ki}]$
- Sum of matrices $\mathbf{A}$ and $\mathbf{B}$ of the same size
  - $\mathbf{A} + \mathbf{B} = [a_{ik}] + [b_{ik}] = [a_{ik} + b_{ik}]$
- Scalar multiple of matrix $\mathbf{A}$:
  - $\alpha\mathbf{A} = \alpha[a_{ik}] = [\alpha a_{ik}]$

Matrix-vector multiplication

$$\mathbf{Ax} = \begin{pmatrix} a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & a_{22} & \dots & a_{2n} \\ \vdots & \vdots & & \vdots \\ a_{m1} & a_{m2} & \dots & a_{mn} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix} = \begin{pmatrix} \sum_{j=1}^{n} a_{1j} x_j \\ \sum_{j=1}^{n} a_{2j} x_j \\ \vdots \\ \sum_{j=1}^{n} a_{mj} x_j \end{pmatrix} = \mathbf{b}$$

Symbolically

$$\begin{pmatrix} \times \\ \times \\ \times \\ \times \end{pmatrix} = \begin{pmatrix} \leftarrow & - & - & \rightarrow \\ \leftarrow & - & - & \rightarrow \\ \leftarrow & - & - & \rightarrow \\ \leftarrow & - & - & \rightarrow \end{pmatrix} \begin{pmatrix} \uparrow \\ | \\ | \\ \downarrow \end{pmatrix}$$

In practice

$$\begin{pmatrix} 2 & 3 \\ 6 & 4 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} 5 \\ -2 \end{pmatrix} = \begin{pmatrix} ? \\ ? \\ ? \end{pmatrix}$$

$$\begin{pmatrix} 2 & 3 \\ 6 & 4 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} 5 \\ -2 \end{pmatrix} = \begin{pmatrix} 2 \cdot 5 + 3 \cdot (-2) \\ 6 \cdot 5 + 4 \cdot (-2) \\ 1 \cdot 5 + 0 \cdot (-2) \end{pmatrix} = \begin{pmatrix} 4 \\ 22 \\ 5 \end{pmatrix}$$

Or

$$\begin{pmatrix} 2 & 3 \\ 6 & 4 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} 5 \\ -2 \end{pmatrix} = 5 \cdot \begin{pmatrix} 2 \\ 6 \\ 1 \end{pmatrix} - 2 \cdot \begin{pmatrix} 3 \\ 4 \\ 0 \end{pmatrix} = \begin{pmatrix} 4 \\ 22 \\ 5 \end{pmatrix}$$

Alternative presentation of matrix-vector multiplication:

Denote the column vectors of the matrix $\mathbf{A}$ by $\mathbf{a_j}$. Then

$$\mathbf{b} = \mathbf{A}\mathbf{x} = (\mathbf{a}_1\mathbf{a}_2 \ldots \mathbf{a}_n) \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix} = \sum_{j=1}^{n} x_j \mathbf{a}_j$$

- The vector $\mathbf{b}$ is a **linear combination** of the columns of $\mathbf{A}$.
- The *column space* of $\mathbf{A}$ consists of all vectors $\mathbf{b}$ that can be stated as linear combinations of columns of $\mathbf{A}$.

Solving a set of linear equations

$$\mathbf{Ax} = \begin{pmatrix} a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & a_{22} & \dots & a_{2n} \\ \vdots & \vdots & & \vdots \\ a_{m1} & a_{m2} & \dots & a_{mn} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix} = \begin{pmatrix} \sum_{j=1}^{n} a_{1j}x_j \\ \sum_{j=1}^{n} a_{2j}x_j \\ \vdots \\ \sum_{j=1}^{n} a_{mj}x_j \end{pmatrix} = \mathbf{b}$$

If x_i's are unknown, this represents a system of linear equations

$$\begin{array}{llll} a_{11}x_1 & +a_{12}x_2 & +\ldots + a_{1n}x_n & = & b_1 \\ a_{21}x_1 & +a_{22}x_2 & +\ldots + a_{2n}x_n & = & b_2 \\ \vdots & & & & \\ a_{m1}x_1 & +a_{m2}x_2 & +\ldots + a_{mn}x_n & = & b_m \end{array}$$

Solving a set of linear equations

- Matrix notation becomes handy when a system of linear equations is solved
- Use Gaussian elimination to transform an *augmented* matrix $[\mathbf{A}|\mathbf{b}]$ to *row echelon form*
- Use *back substitution* to solve the system

Solving a set of linear equations

$$\begin{aligned} x_1 \quad +2x_2 \quad +x_3 &= \quad 3 \\ 3x_1 \quad -x_2 \quad -3x_3 &= -1 \\ 2x_1 \quad +3x_2 \quad +x_3 &= \quad 4 \end{aligned}$$

- Augmented matrix

$$\begin{pmatrix} 1 & 2 & 1 & 3 \\ 3 & -1 & -3 & -1 \\ 2 & 3 & 1 & 4 \end{pmatrix}$$

Row echelon form

- A matrix is in row echelon form if

1. The first nonzero entry in each row is 1
2. If row k does not consist entriely of zeros, the number of leading zero entries in row $k+1$ is greater than the number of leading zero entries in row k
3. If there are rows whose entries are all zero, they are below the rows having nonzero entries

$$\begin{pmatrix} 1 & 4 & 2 \\ 0 & 1 & 3 \\ 0 & 0 & 1 \end{pmatrix}$$

Gaussian elimination

- Elementary row operations to transform a matrix to row echelon form:
  1. Interchange two rows
  2. Multiply a row by a nonzero real number
  3. Replace a row by its sum with a multiple of another row

$$\begin{pmatrix} \underline{1} & 2 & 1 & 3 \\ 3 & -1 & -3 & -1 \\ 2 & 3 & 1 & 4 \end{pmatrix} \rightarrow \begin{pmatrix} 1 & 2 & 1 & 3 \\ 0 & -7 & -6 & -10 \\ 0 & -1 & -1 & -2 \end{pmatrix} \rightarrow$$

Gaussian elimination

$$\begin{pmatrix} 1 & 2 & 1 & 3 \\ 0 & \underline{-7} & -6 & -10 \\ 0 & -1 & -1 & -2 \end{pmatrix} \rightarrow \begin{pmatrix} 1 & 2 & 1 & 3 \\ 0 & 1 & 6/7 & 10/7 \\ 0 & 0 & \underline{-1/7} & -4/7 \end{pmatrix} \rightarrow \begin{pmatrix} 1 & 2 & 1 & 3 \\ 0 & 1 & 6/7 & 10/7 \\ 0 & 0 & 1 & 4 \end{pmatrix}$$

- By backsubstitution:

$$\begin{aligned} x_3 &= 4 \\ x_2 &= 10/7 - 6/7 * 4 &&= -2 \\ x_1 &= 3 - 2 * (-2) - 4 &&= 3 \end{aligned}$$

Reduced row echelon form

- Matrix $\mathbf{A}$ is in *reduced row echelon form* if

  1. $\mathbf{A}$ is in row echelon form
  2. All other elements of the column in which the leading entry 1 occurs are equal to zero.

- From a reduced row echelon form of the augmented matrix a solution can be directly read (if the system is consistent and fully determined)

$$\begin{pmatrix} 1 & 0 & 0 & 5 \\ 0 & 1 & 0 & 4 \\ 0 & 0 & 1 & 2 \end{pmatrix}$$

Reduced row echelon form

- Gauss-Jordan reduction to transform matrix $\mathbf{A}$ to reduced row echelon form by using elementary row operations:

1. Sort the rows of $\mathbf{A}$ so that upper rows have fever than or the same number of zero entries before the first nonzero entry as the lower rows.
2. Let $i = 1$; Repeat until i'th row R_i contains only zeros.
   (a) Multiply the row R_i of $\mathbf{A}$ by $1/a_{ik}$, where a_{ik} is the first nonzero element of R_i. ($a_{ik} \leftarrow 1$)
   (b) For all rows R_j, $j \neq i$: Substract $a_{jk}R_i$ from R_j. ($a_{jk} \leftarrow 0$)
   (c) $i = i + 1$

Consistency

- If a linear equation system has at least one solution, it is said to be *consistent*. Otherwise the system is *inconsistent*.

- Linear equation system $\mathbf{Ax} = \mathbf{b}$ is consistent if and only if $\mathbf{b}$ is in the column space of $\mathbf{A}$. Otherwise the system is inconsistent.

- For an inconsistent system one can look for a solution $\hat{\mathbf{x}}$ minimizing the norm of residual vector $\mathbf{A}\hat{\mathbf{x}} - \mathbf{b}$

Vector norms

The most common vector norms are

- 1-norm: $\|\mathbf{x}\|_1 = \sum_{i=1}^{n} |x_i|$
- Euclidean norm: $\|\mathbf{x}\|_2 = \sqrt{\sum_{i=1}^{n} x_i^2}$
- max-norm: $\|\mathbf{x}\|_\infty = \max_{1 \leq i \leq n} |x_i|$
- all of the above are special cases of the L_p-norm (or p-norm): $\|\mathbf{x}\|_p = (\sum_{i=1}^{n} x_i^p)^{1/p}$

Linear Independence

- Given a set of vectors $(\mathbf{v}_j)_{j=1}^n$ in $\mathbb{R}^m$, $m \geq n$, consider the set of linear combinations $y = \sum_{j=1}^n \alpha_j \mathbf{v}_j$ for arbitrary coefficients α_j.

- The vectors $(\mathbf{v}_j)_{j=1}^n$ are **linearly independent**, if $\sum_{j=1}^n \alpha_j \mathbf{v}_j = 0$ if and only if $\alpha_j = 0$ for all $j = 1, ..., n$.

- A set of m linearly independent vectors of $\mathbb{R}^m$ is called a **basis** in $\mathbb{R}^m$: any vector in $\mathbb{R}^m$ can be expressed as a linear combination of the basis vectors.

Example

The column vectors of the matrix

$$[\mathbf{v}_1\ \mathbf{v}_2\ \mathbf{v}_3\ \mathbf{v}_4] = \begin{pmatrix} 1 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 1 \end{pmatrix}$$

are not linearly independent, as

$$\alpha_1\mathbf{v}_1 + \alpha_2\mathbf{v}_2 + \alpha_3\mathbf{v}_3 + \alpha_4\mathbf{v}_4 = 0$$

holds for $\alpha_1 = \alpha_3 = 1$, $\alpha_2 = \alpha_4 = -1$.

Rank of a matrix

- The **rank** of a matrix is the maximum number of linearly independent column vectors.
  - rank of a matrix = dimension of a subspace span by the columns (rows) of the matrix

- A square matrix $\mathbf{A} \in \mathbb{R}^{n \times n}$ with rank n is called **nonsingular**, and it has an **inverse** $\mathbf{A}^{-1}$ satisfying $\mathbf{A}\mathbf{A}^{-1} = \mathbf{A}^{-1}\mathbf{A} = \mathbf{I}$.
  - For linear equation system $\mathbf{A}\mathbf{x} = \mathbf{b}$, $\mathbf{x} = \mathbf{A}^{-1}\mathbf{b}$
  - Moore-Penrose pseudoinverse generalizes the result for $m \times n$ matrices.
  - Least squares solution for inconsistent system.

Example

The 4×4 matrix

$$\begin{pmatrix} 1 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 1 \end{pmatrix}$$

has rank 3.

Nullspace of the matrix

- The **nullspace** $N(\mathbf{A})$ of matrix $\mathbf{A}$ is a set of all solutions to the homogeneous system $\mathbf{Ax} = 0$.
  - $N(\mathbf{A}) = \{\mathbf{x} \in R^n | \mathbf{Ax} = 0\}$

- The dimension of nullspace (rank of matrix spanning the nullspace) is called **nullity**.

Let $\mathbf{A}$ be an $m \times n$ matrix. Then $rank(\mathbf{A}) + N(\mathbf{A}) = n$.

Fully determined linear equation systems

- Let $\mathbf{Ax} = \mathbf{b}$ define a linear equation system, $\mathbf{A}$ is $m \times n$ matrix.
- Linear equation system is *fully determined* if $rank(\mathbf{A}) = n$. Then, the nullity of $\mathbf{A} = 0$, and the linear equation system has a unique (least squares) solution.
- In Gaussian elimination, n pivoting operations possible.

Underdetermined linear equation systems

- Linear equation system is *underdetermined* if $rank(\mathbf{A}) < n$. Then, the nullity of $\mathbf{A} > 0$, and the linear equation system has infinitely many (least squares) solutions.
  - Any vector from the null space can be added to the solution to obtain a new one.
  - Fever independent equations than unknowns. We have $n - rank(\mathbf{A})$ *free variables* that we can assign arbitrary values and solve for other, *dependent variables*.
  - Only $rank(\mathbf{A})$ pivoting operations possible for $\mathbf{A}$ in Gaussian elimination.

Examples

$$\begin{array}{rrrr} x_1 & +2x_2 & +x_3 = & 3 \\ 3x_1 & -x_2 & -3x_3 = & -1 \\ 2x_1 & +3x_2 & +x_3 = & 4 \end{array}$$

$$\begin{pmatrix} 1 & 2 & 1 \\ 3 & -1 & -3 \\ 2 & 3 & 1 \end{pmatrix} * \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 3 \\ -1 \\ 4 \end{pmatrix}$$

- Rank of $\mathbf{A} = 3$, fully determined, unique solution $(x_1 = 3, x_2 = -2, x_3 = 4)$.

Examples

$$\begin{array}{cccc} x_1 & +2x_2 & +x_3 = & 3 \\ 3x_1 & -x_2 & -3x_3 = & -1 \end{array}$$

$$\begin{pmatrix} 1 & 2 & 1 \\ 3 & -1 & -3 \end{pmatrix} * \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 3 \\ -1 \end{pmatrix}$$

- Rank of $\mathbf{A} = 2$, underdetermined, also e.g. $(x_1 = 16/7, x_2 = -8/7, x_3 = 3)$ is a solution.

Examples

$$\begin{array}{rrrr} x_1 & +2x_2 & +x_3 = & 3 \\ 3x_1 & -x_2 & -3x_3 = & -1 \\ 4x_1 & +x_2 & -2x_3 = & 2 \end{array}$$

$$\begin{pmatrix} 1 & 2 & 1 \\ 3 & -1 & -3 \\ 4 & 1 & -2 \end{pmatrix} * \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 3 \\ -1 \\ 2 \end{pmatrix}$$

- Rank of $\mathbf{A} = 2$, underdetermined. Why?

Examples

$$\begin{array}{rrrr} x_1 & +2x_2 & +x_3 = & 3 \\ 3x_1 & -x_2 & -3x_3 = & -1 \\ 2x_1 & +3x_2 & +x_3 = & 4 \\ 3x_1 & +6x_2 & +3x_3 = & 8 \end{array}$$

$$\begin{pmatrix} 1 & 2 & 1 \\ 3 & -1 & -3 \\ 2 & 3 & 1 \\ 3 & 6 & 3 \end{pmatrix} * \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 3 \\ -1 \\ 4 \\ 8 \end{pmatrix}$$

- Rank of $\mathbf{A} = 3$, fully determined, inconsistent. Why?

Examples

$$\begin{array}{cccc} x_1 & +2x_2 & +x_3 = & 3 \\ 3x_1 & -x_2 & -3x_3 = & -1 \\ 4x_1 & +x_2 & -2x_3 = & 1 \end{array}$$

$$\begin{pmatrix} 1 & 2 & 1 \\ 3 & -1 & -3 \\ 4 & 1 & -2 \end{pmatrix} * \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} 3 \\ -1 \\ 1 \end{pmatrix}$$

- Rank of $\mathbf{A} = 2$, underdetermined, inconsistent. Why?

Condition number

- For any $a \neq 1$ the matrix $\mathbf{A} = \begin{pmatrix} a & 1 \\ 1 & 1 \end{pmatrix}$ is nonsingular and has the inverse $\mathbf{A}^{-1} = \frac{1}{a-1} \begin{pmatrix} 1 & -1 \\ -1 & a \end{pmatrix}$.
- As $a \to 1$, the norm of $\mathbf{A}^{-1}$ tends to infinity.
- Nonsingularity is not always enough!
- Define the **condition number** of a matrix to be $\kappa(A) = \|\mathbf{A}\| \|\mathbf{A}^{-1}\|$.
- Large condition number means trouble!

Orthogonality

- Two vectors $\mathbf{x}$ and $\mathbf{y}$ are **orthogonal**, if $\mathbf{x}^T\mathbf{y} = 0$.
- Let $\mathbf{q}_j$, $j = 1, \ldots, n$ be orthogonal, i.e. $\mathbf{q}_i^T\mathbf{q}_j = 0$, $i \neq j$. Then they are linearly independent. (Proof?)
- Let the set of orthogonal vectors $\mathbf{q}_j$, $j = 1, \ldots, m$ in $\mathbb{R}^m$ be normalized, $\|\mathbf{q}\| = 1$. Then they are **orthonormal**, and constitute an **orthonormal basis** in $\mathbb{R}^m$.
- A matrix $\mathbb{R}^{m\times m} \ni \mathbf{Q} = [\mathbf{q}_1\ \mathbf{q}_2\ \ldots\ \mathbf{q}_m]$ with orthonormal columns is called an **orthogonal matrix**.

Why we like orthogonal matrices

- An orthogonal matrix $\mathbf{Q} \in \mathbb{R}^{m \times m}$ has rank m (since its columns are linearly independent).

- $\mathbf{Q}^T\mathbf{Q} = \mathbf{I}$. $\mathbf{Q}\mathbf{Q}^T = \mathbf{I}$. (Proofs?)

- The inverse of an orthogonal matrix $\mathbf{Q}$ is $\mathbf{Q}^{-1} = \mathbf{Q}^T$.

- The Euclidean length of a vector is invariant under an orthogonal transformation $\mathbf{Q}$: $\|\mathbf{Q}\mathbf{x}\|^2 = (\mathbf{Q}\mathbf{x})^T\mathbf{Q}\mathbf{x} = \mathbf{x}^T\mathbf{x} = \|\mathbf{x}\|^2$.

- The product of two orthogonal matrices $\mathbf{Q}$ and $\mathbf{P}$ is orthogonal:

$$\mathbf{X}^T\mathbf{X} = (\mathbf{P}\mathbf{Q})^T\mathbf{P}\mathbf{Q} = \mathbf{Q}^T\mathbf{P}^T\mathbf{P}\mathbf{Q} = \mathbf{Q}^T\mathbf{Q} = \mathbf{I}.$$

References

[1] Lars Eldén: Matrix Methods in Data Mining and Pattern Recognition, SIAM 2007.

[2] G. H. Golub and C. F. Van Loan. Matrix Computations. 3rd ed. Johns Hopkins Press, Baltimore, MD., 1996.