Bioeng 261 Lecture 08 2017

Flux balance analysis Cont'd.

(& constraint based analysis)

- Null spaces
- Spans
- Geometry & constraints
- Optimality conditions & optimisation problems

$\left.\begin{matrix}\text{Null spaces}\\ \text{Spans}\end{matrix}\right\}$ Linear algebra

$\left.\begin{matrix}\text{Geometry \& constraints}\\ \text{Optimality conditions \& optimisation problems}\end{matrix}\right\}$ Linear programming

Null spaces (Linear algebra).

The nullspace for a matrix $\underline{A}$ is the set of all solutions to $\underline{A}\bar{x} = \bar{0}$

Zero is always in the null space: $\underline{A}\,\bar{0} = \bar{0}$

A non-trivial nullspace is when we have non-zero solutions

eg $\begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$

ie

$$\left.\begin{aligned} &(1)\quad x_1 - x_2 = 0 \Rightarrow x_1 = x_2 \\ &(2)\quad -x_1 + x_2 = 0 \Rightarrow x_1 = x_2 \end{aligned}\right\}\ \text{same equations}$$

$\left.\begin{matrix}\cdot\ 2\ \text{unknowns}\\ \cdot\ 1\ \text{indep. constraint}\end{matrix}\right\}$ $\Rightarrow 2-1=1$ free var.

$\left.\begin{matrix}\text{free choice of } x_2 \text{ (say)}\\ \text{then determines } x_1\end{matrix}\right\}$ or vice-versa

$$\boxed{N(A) = \left\{ \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \,\middle|\, x_1 = x_2 \right\}}$$

Mathematically, elements (vectors)

Null space of A $= N(A) = \{ \bar{x} \mid \underline{A}\bar{x} = \bar{0} \}$

set of — such that — condition

Example

$$\underline{S} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 2 & -1 & -2 & 0 & 0 & 0 \\ 0 & 0 & 3 & -3 & 3 & 0 \\ 0 & 0 & 0 & 1 & -1 & 1 \end{bmatrix}$$

Goal: $N(\underline{S}) = \{ \bar{J} \mid \underline{S}\bar{J} = \bar{0} \}$

ie Need to solve $\boxed{\underline{S}\bar{J} = \bar{0}}$

→ usually choose 'free' variables to parameterise the null space with

Example Cont'd

expect $N-M=2$ free vars.

$$\begin{array}{cc} & N=6 \\ M=4 & \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 2 & -1 & -2 & 0 & 0 & 0 \\ 0 & 0 & 3 & -3 & 3 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix} \end{array}$$

row operations:

$$\left.\begin{array}{l} r_1 \to r_1 \\ r_2 \to r_2 + 2r_1 \\ r_3 \to r_3 \\ r_4 \to r_4 \end{array}\right\} \text{to make upper triangular}$$

$$\Rightarrow \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & -2 & 0 & 0 & 0 \\ 0 & 0 & 3 & -3 & 3 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix} \bar{J} = \bar{0}$$

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ie
$$\begin{aligned} -J_1 + J_2 &= 0 \\ J_2 - 2J_3 &= 0 \\ \cancel{3}J_3 - \cancel{3}J_4 + \cancel{3}J_5 &= 0 \\ J_4 - J_5 - J_6 &= 0 \end{aligned}$$

4 equations, 6 vars.

choose 2: eg J_1, J_5 & write others in terms of these

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eg $J_1 = 2, J_5 = 0$

$$\bar{J}^{(1)} = \begin{pmatrix} 2 \\ 2 \\ 1 \\ 1 \\ 0 \\ 1 \end{pmatrix}$$

OR $J_1 = 0, J_5 = 1$

$$\bar{J}^{(2)} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}$$

& $\boxed{N(\underline{S}) = \mathrm{span}\{ \bar{J}^{(1)}, \bar{J}^{(2)} \}}$

Span?: all linear combinations of a set of vectors

Here:

$$\underbrace{N(\underline{S})}_{\text{null space}} = \text{span}\Big\{\underbrace{\text{independent vectors solving } \underline{S}\,\bar{J} = \bar{0}}_{\text{same number as number free vars}}\Big\}$$

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eg $\boxed{N(\underline{S}) = \text{span}\{\bar{J}^{(1)}, \bar{J}^{(2)}\}}$

where $\bar{J}^{(1)} = \begin{pmatrix} 2 \\ 2 \\ 1 \\ 1 \\ 0 \\ 1 \end{pmatrix}$, $\bar{J}^{(2)} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}$

Steps: reduce to minimal set of eqns

choose free vars (eg m−n of them)

find set of indep. vectors

write $N(\underline{S}) = \text{span}\{\ \}$

Boundary vs Internal Fluxes

Sometimes we want to draw 'system boundaries' & call some fluxes 'boundary' fluxes & some 'internal' fluxes.

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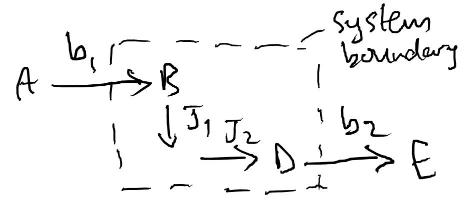
eg



b: boundary
J: internal
(fluxes)

We can either include these as usual

$$\begin{array}{c|c} & J_1 \quad J_2 \quad b_1 \quad b_2 \\ \begin{matrix} A \\ B \\ C \\ D \\ E \end{matrix} & \begin{bmatrix} 0 & 0 & -1 & 0 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

(include b in $\bar{J}$)

OR

focus on internal

$$\begin{array}{c|c} & J_1 \quad J_2 \\ \begin{matrix} B \\ C \\ D \end{matrix} & \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix} \end{array}$$

In this later case we can write

$\boxed{\underline{S}\,\bar{J} \geq 0}$, if we choose signs carefully.

$(\underline{S}\,\bar{J} = \bar{b}_{net} \geq 0)$

Geometry: Nullspace vs Feasible region

$\underbrace{\text{Nullspace}}_{=}$ vs $\underbrace{\text{Feasible region}}_{\geq}$

The two forms

$\underbrace{\underline{S}\bar{J} = \bar{0}}_{\text{all fluxes}}$ or $\underbrace{\underline{S}\bar{J} \geq 0}_{\text{subset of fluxes eg internal only.}}$

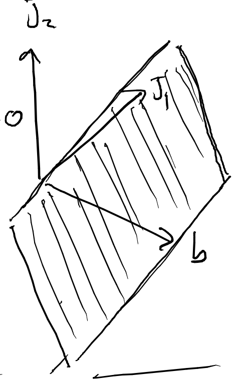
are equivalent but have slightly different geometric pictures

$\underline{S}\bar{J} = \bar{0}$

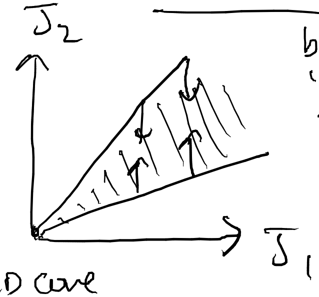
eg

$J_2 - J_1 + b = 0$

2D plane in 3D.



$\underline{S}\bar{J} \geq \bar{0}$ eg $2J_1 - J_2 \geq 0$, $J_2 - \frac{1}{2}J_1 \geq 0$



b becomes 'slack' variable

2D cone

3 vars

1 indep equality constr.

$3 - 1 = 2$ dimensional (hyper-) plane

| nullspace |

2 vars

2 indep. inequality constraints

2D cone/polyhedra

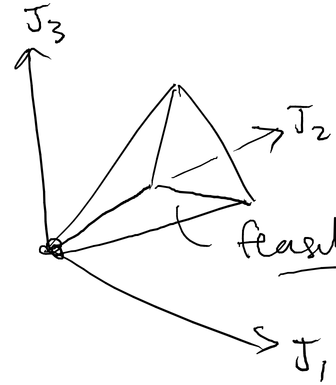
| feasible region |

What? Why?

In general we will put in 'standard form'

$\boxed{\underline{S}\bar{J} = \bar{0}}$ & use | nullspace | (include boundary fluxes)

But you may see pictures like:



(all internal)

feasible region

which come from inequality constraints version.

→ Just be aware

(General principle/trade-off: simple in higher dim or complex in lower d)

'Special' solutions: uniqueness?

- Regardless of specific form used, we have $\boxed{\text{linear constraints}}$ on $\boxed{\text{fluxes}}$ $\bar{J}$

(Note: would typically be non-linear in concentrations if using mass action)

The constraints can be thought of as

- Defining a non-trivial null space ($\underline{S}\,\bar{J} = \bar{0}$ form)

or

- A polyhedral feasible region ($\underline{S}\,\bar{J} \geq \bar{0}$ form for internal)

$\Rightarrow$ either way we might want to look at ways to 'pick out' particular solutions from these sets of solutions.

Constraints & Optimality conditions

We can add many types of extra constraints or conditions to narrow down possible sol^ns:

- bounds/signs of fluxes
- thermodynamic feasibility (directional constraints)
- optimality or extreme cases (eg max. energy prod.)

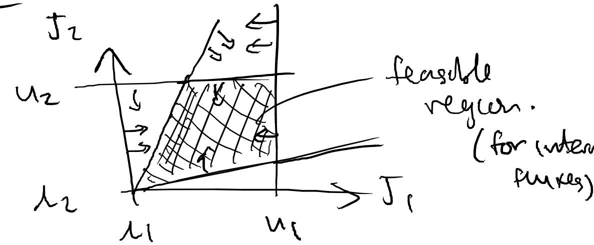
The most natural to include first in general are lower & upper flux bounds, ie

$\boxed{\text{capacity constraints}}$:

$$\boxed{l_i \leq J_i \leq u_i}$$

(note: without these only know ratios)

Gives



For irreversible, use $\boxed{J_i \geq 0}$ (why?)

'Optimal' solutions

A useful way to pick out 'special' solutions is to use **optimality** (max/min) conditions

- these tell us about limits on what is possible

eg 'maximal rate of ATP production is...'

Note:

- a real system may or may not reach these limits!
  - many competing goals so may not be optimal for any one
  - still a good way to predict/understand
  - many sensible constraints can be rewritten as max/min conditions.

Example: cont'd

Recall our example where we wrote our 2D null space in terms of J_1 & J_5

$$\boxed{\begin{aligned} J_2 &= J_1 \\ J_3 &= J_1/2 \\ J_4 &= J_1/2 + J_5 \\ J_6 &= J_1/2 \end{aligned}}$$

ie

$J_2, J_3, J_4, J_6 = f(J_1, J_5)$

6 vars, 2 free
4 det.

can write as $\underset{\sim}{S}\bar{J} = \bar{0}$

To find a particular sol^n.

- suppose $2 \leq J_1, J_5 \leq 10$ bounds apply to both
- $J_i \geq 0$ for all i
- J_4 is ATP production & J_6 is lactate prod. } for example

Goals Case 1. Max ATP prod.

Case 2. Max ATP prod. while minimising lactate prod.

Case I.

$$\boxed{\begin{array}{l} \underline{\max}\ J_4 \\ \text{subject to} \\ \bullet\quad \underline{S}\,\bar{J} = \bar{0} \\ \& \\ \bullet\quad 2 \le J_1 \le 10 \\ \bullet\quad 2 \le J_5 \le 10 \end{array}}$$

$\underline{S}\,\bar{J} = \bar{0} \iff$ we re-wrote as
$$\begin{cases} J_2 = J_1 \\ J_3 = J_1/2 \\ J_4 = J_1/2 + J_5 \\ J_6 = J_1/2 \end{cases}$$

Sol^n: want $J_4 = \frac{J_1}{2} + J_5$ max.

$\Rightarrow$ set $\boxed{J_1 = J_5 = 10}$ (can vary indep.)

$\Rightarrow \boxed{J_4 = 15}$

Case 2

$$\boxed{\begin{array}{l} \underline{\max}\ aJ_4 - bJ_6 \\ \quad a, b > 0 \text{ weights} \\ \quad (\text{'values' or 'costs'}) \\ \text{s.t. same constraints} \end{array}}$$

$\max -J \equiv \min J$

$$\underline{\max}\quad aJ_4 - bJ_6 = \frac{(a-b)}{2}J_1 + aJ_5$$

- if $a > b$: same: $J_1 = J_5 = 10$
- if $a < b$: $J_1 = 2$, $J_5 = 10$
- if $a = b$: $J_1 = ?$, $J_5 = 10$ — not enough info for unique

General Optimisation Framework

$$\min\quad z = \bar{c}^T \bar{J} \quad \text{objective function}$$

$$\left.\begin{array}{l} \text{s.t.}\quad \underline{S}\,\bar{J} = 0 \\ \qquad l_i \le \bar{J}_i \le u_i \end{array}\right\} \text{constraints}$$

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z : scalar (number)

$\bar{c}$: vector of weights (here, 'costs')

eg

$$\bar{c}^T \bar{J} = \begin{pmatrix} 1 & 2 & -1 \end{pmatrix} \begin{pmatrix} J_1 \\ J_2 \\ J_3 \end{pmatrix}$$

$$= J_1 + 2J_2 - J_3 = z$$

Linear objective function + Linear constraints } "Linear Programming"

What should I be able to do?

- Given network find $\underline{S}$
- Find <u>nullspace</u> for simple $\underline{S}$
  - L reduce to indep. eq^n's
  - L choose free fluxes
  - L find indep. vectors
  - L write as span{ }
- Describe typical/useful additional constraints
- Write down optimisation problems for given description
- Solve very simple optimisation problems