



8. Geometry of the flux cone

- ▷ **Convex cone**
- $C \subseteq \mathbb{R}^n$, with $\lambda x + \mu y \in C$ whenever $x, y \in C$ and $\lambda, \mu \geq 0$.
- ▷ **Polyhedral cone** **Outer**
- $C = \{x \in \mathbb{R}^n \mid Ax \geq 0\}$, for some $A \in \mathbb{R}^{m \times n}$.
- ▷ **Finitely generated cone** **Inner**
- $C = \text{cone}\{g^1, \dots, g^s\} = \{\lambda_1 g^1 + \dots + \lambda_s g^s \mid \lambda_1, \dots, \lambda_s \geq 0\}$,
- for some $g^1, \dots, g^s \in \mathbb{R}^n$.
- ▷ **Theorem** (Farkas-Minkowski-Weyl)
A convex cone is polyhedral iff it is finitely generated.



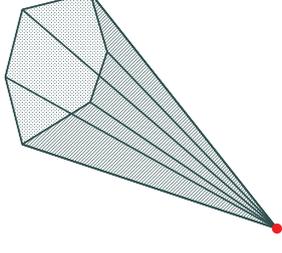
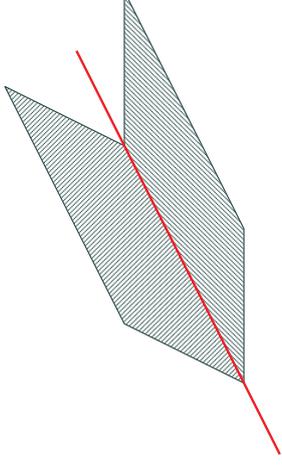
Pointed cones

- ▷ **C** pointed polyhedral cone
 - ▷ $r \in C$ is an **extreme ray** if there exist no linearly independent $r', r'' \in C$ such that $r = r' + r''$ (identify $r^1, r^2 \in C$ if $r^1 = \lambda r^2$, for some $\lambda > 0$).
 - ▷ **Theorem.** If C is pointed, then
- $$C = \text{cone}\{r^1, \dots, r^s\} = \{\lambda_1 r^1 + \dots + \lambda_s r^s \mid \lambda_1, \dots, \lambda_s \geq 0\},$$
- where r^1, \dots, r^s are the **extreme rays** of C .
- ▷ This representation is **minimal** and **unique** up to multiplication with positive scalars.



Pointed vs. non-pointed cones

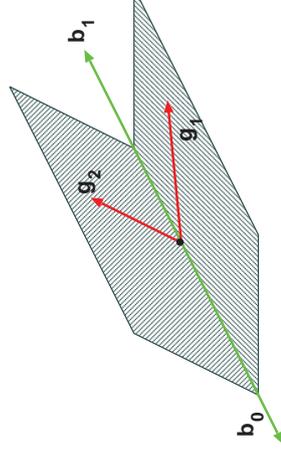
- ▷ Polyhedral cone $C = \{x \in \mathbb{R}^n \mid Ax \geq 0\}$
- ▷ **Lineality space** $\text{linsp}(C) = \{x \in \mathbb{R}^n \mid Ax = 0\}$
- ▷ **C is pointed** if $\text{linsp}(C) = \{0\}$.



Non-pointed cones

- ▷ **C** polyhedral cone, $t = \dim(\text{linsp}(C)) \geq 0$
- ▷ Faces G of dimension $t + 1$ are called **minimal proper faces**.
- ▷ **Theorem.** If $g^i \in G^i \setminus \text{linsp}(C)$, for $i = 1, \dots, s$, and $\text{linsp}(C) = \text{cone}\{b^0, \dots, b^t\}$, then

$$C = \text{cone}\{g^1, \dots, g^s, b^0, \dots, b^t\}$$



- ▷ For non-pointed cones, this representation is still **minimal**, but **not unique**.



Inner descriptions of the flux cone

- ▷ **Idea:** Make the cone pointed in case it is not.
- ▷ Split reversible reactions into two irreversible reactions
 ~> pointed cone in a higher-dimensional space
 ~> compute the extreme rays
- ▷ Split all reversible reactions ~> **extremal currents** (Clarke 80)
- ▷ Split all internal reversible reactions ~> **extreme pathways** (Palsson et al., 2000)
- ▷ Alternatively, consider all flux vectors with minimum support in the original cone ~> **elementary flux modes** (Schuster et al. 94)

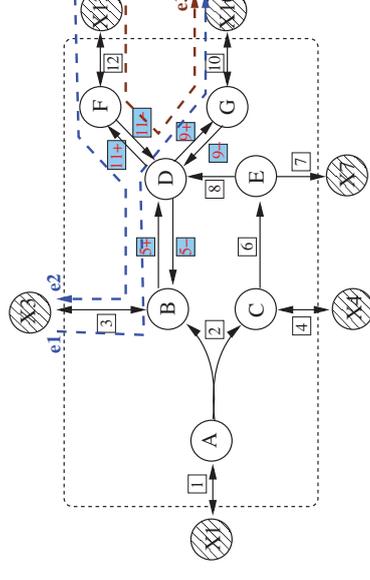


Example (ctd)

- ▷ e^1, e_r^2, e^3 are extreme pathways in the reconfigured space, whereas in the original space $e^3 = e^1 + e^2$.
- ▷ The reason is that the reversible reaction 5 is split in the two irreversible reactions 5^+ and 5^- .
- ▷ The number of elementary flux modes is 18, while the number of extreme pathways (after reconfiguration) is 14.



Example



$$\begin{aligned}
 e^1 &= (0, 0, 1, 0, 1, 0, 0, 0, 0, 1, 1, 0, 0, 0) \\
 e_r^1 &= (0, 0, 1, 0, 1, 0, 0, 0, 0, 1, 0, 1, 0, 0, 0) \\
 e^2 &= (0, 0, -1, 0, -1, 0, -1, 0, 0, 0, 0, 0, -1, -1) \\
 e_r^2 &= (0, 0, -1, 0, 0, 1, 0, 0, 0, 0, 0, 0, 1, -1) \\
 e^3 &= (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 1, -1, -1, -1) \\
 e_r^3 &= (0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 1, 0, 1, -1)
 \end{aligned}$$



Mathematical results

Theorem

- ▷ Extreme pathways correspond to a subset of the elementary modes (up to 2-cycles).
- ▷ Elementary modes are equivalent to extremal currents (up to 2-cycles).

Corollary

Elementary modes and extreme pathways can be computed by algorithms that enumerate the extreme rays of a pointed cone.

Software: `efmtool` (<http://www.csb.ethz.ch/tools/efmtool>)



| Inner description | Split react. | Reconfigured flux cone C' | | | Properties | |
|-------------------|--------------|-----------------------------|----------------------------|--------------------|--------------|--------|
| | | Dim. | # Constraints | $\text{linsp}(C')$ | Unique | Minim. |
| Extr. pathways | Rev_{int} | $n + Rev_{int} $ | $m + lrr + 2 Rev_{int} $ | $\{0\}$ | \checkmark | yes |
| Extr. currents | Rev | $n + Rev $ | $m + lrr + 2 Rev $ | $\{0\}$ | \checkmark | yes |
| Elem. modes | \emptyset | n | $m + lrr $ | $\text{linsp}(C)$ | \checkmark | no |



Larhlimi/Bockmayr'09

| Metabolic network | Met | lrr | Rev | EFM | EP | s | t |
|------------------------------|-----|-----|-----|-------|-------|----|----|
| Glycolysis / Gluconeogenesis | 32 | 18 | 29 | 19464 | 1745 | 16 | 13 |
| Citrate cycle (TCA cycle) | 22 | 4 | 25 | 3870 | 1588 | 4 | 12 |
| Pentose phosphate pathway | 34 | 19 | 24 | 5155 | 1630 | 19 | 8 |
| Pentose and glucuronate | 50 | 13 | 46 | 2258 | 231 | 7 | 23 |
| Fructose and mannose | 46 | 37 | 31 | 2411 | 2102 | 30 | 6 |
| Galactose | 41 | 22 | 28 | 623 | 524 | 13 | 9 |
| Starch and sucrose | 47 | 35 | 30 | 2097 | 1718 | 30 | 5 |
| Pyruvate | 28 | 40 | 29 | 47708 | 27390 | 37 | 16 |
| Propanoate | 34 | 20 | 29 | 877 | 233 | 17 | 13 |
| Butanoate | 40 | 23 | 30 | 2138 | 541 | 18 | 11 |
| Nitrogen | 41 | 53 | 14 | 601 | 612 | 44 | 9 |
| Sulfur | 18 | 26 | 4 | 321 | 326 | 28 | 1 |

(s is the number of minimal proper faces and t the dimension of the lineality space)