



## 7. 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.



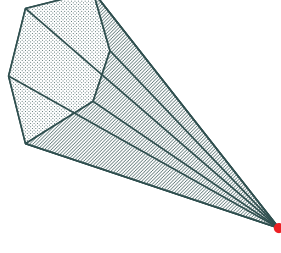
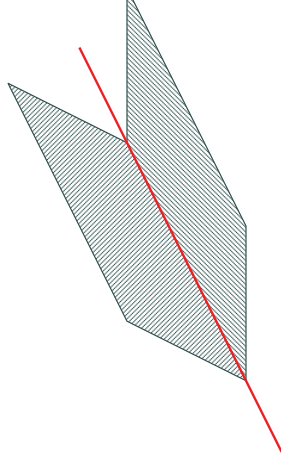
## Pointed cones

- ▷ **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

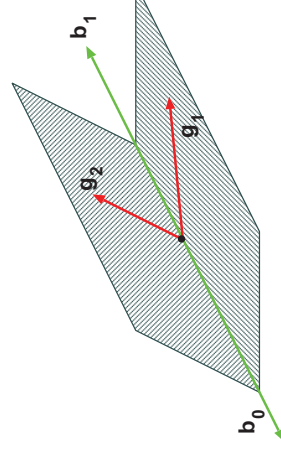
- ▷ Polyhedral cone  $C = \{x \in \mathbb{R}^n \mid Ax \geq 0\}$
- ▷ **Lineality space**  $\text{linsp}(C) = \{x \in \mathbb{R}^n \mid Ax = 0\}$
- ▷ **C is pointed** if  $\text{linsp}(C) = \{0\}$ .



## 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)

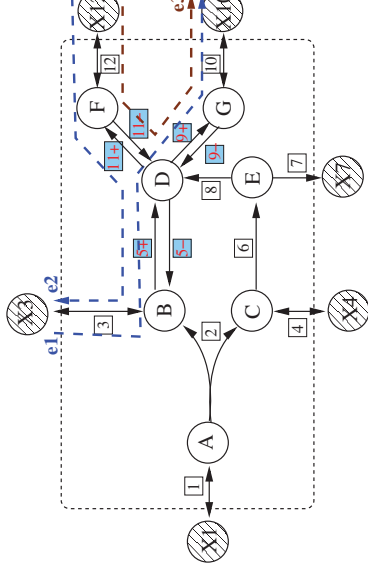


## Example (ctd)

- ▷  $e^1, e_r^2, e^3$  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



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



## 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



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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)