Below, we outline a necessary and sufficient condition for producibility in the context of thermodynamic (irreversibility) constraints. Please refer to the main paper for terminology and mathematical preliminaries.

Lemma 1. *Given $A \in \mathbb{R}^{m \times n}$ and arbitrary $i = 1, \ldots, m$, exactly one of the following two sets is empty (non-empty):*

$$\{w \in \mathbb{R}^n \mid Aw \geq 0,\ (Aw)_i > 0\} \tag{1}$$

$$\{y \in \mathbb{R}^m \mid A^T y = 0,\ y \geq 0,\ y_i > 0\} \tag{2}$$

Lemma 2. *Given $A \in \mathbb{R}^{m \times n}$, arbitrary $i \in 1, \ldots, m$, and $T \subset 1, \ldots, n$, exactly one of the following two sets is empty (non-empty):*

$$\{w \in \mathbb{R}^n \mid Aw \geq 0,\ w_T \geq 0,\ (Aw)_i > 0\} \tag{3}$$

$$\{y \in \mathbb{R}^m \mid y^T A_T \leq 0,\ y^T A_{N \setminus T} = 0,\ y \geq 0,\ y_i > 0\}, \tag{4}$$

where $N = 1, \ldots, n$.

Proof. Applying Lemma 1 to the $(m + |T|) \times n$ matrix $\begin{bmatrix} A \\ (I_T)^T \end{bmatrix}$, shows that exactly one of the following sets is empty (non-empty) for some $i \in 1, \ldots, m$:

$$\{w \in \mathbb{R}^n \mid \begin{bmatrix} A \\ (I_T)^T \end{bmatrix} w \geq 0,\ (Aw)_i > 0\} \tag{5}$$

$$\{y \in \mathbb{R}^m,\ s \in \mathbb{R}^{|T|} \mid \begin{bmatrix} y & s \end{bmatrix}^T \begin{bmatrix} A \\ (I_T)^T \end{bmatrix} = 0,\ y \geq 0,\ s \geq 0,\ y_i > 0\}. \tag{6}$$

Eq. 5 can be rewritten as Eq. 3, while Eq. 6 can be rewritten as:

$$\{y \in \mathbb{R}^m,\ s \in \mathbb{R}^{|T|} \mid y^T A_{N \setminus T} = 0,\ y^T A_T + s = 0,\ y \geq 0,\ s \geq 0,\ y_i > 0\} \tag{7}$$

The set in Eq. 7 is empty (non-empty) if and only if the set in Eq. 4 is empty (non-empty), which proves the lemma. ☐

A species i is producible under nutrient media U, stoichiometry matrix S, and irreversible reactions T if and only if the following set is nonempty:

$$\{u \in \mathbb{R}^{|U|},\ v \in \mathbb{R}^n \mid \bar{S} \begin{bmatrix} u \\ v \end{bmatrix} \geq 0,\ (\bar{S} \begin{bmatrix} u \\ v \end{bmatrix})_i > 0, v_T \geq 0\}, \tag{8}$$

where

$$\bar{S} = \begin{bmatrix} I_U & S \end{bmatrix} \in \mathbb{R}^{m \times (|U| + n)} \quad . \tag{9}$$

Applying Lemma 2 to $\bar{S}$, this is equivalent to the emptiness of:

$$\{g \in \mathbb{R}^m \mid g^T \bar{S}_T \leq 0,\ g^T \bar{S}_{N \setminus T} = 0,\ g \geq 0,\ g_i > 0\}, \tag{10}$$

which can be rewritten as

$$\{g \in \mathbb{R}^m \mid g^T S_T \leq 0,\ g^T S_{N \setminus T} = 0,\ g \geq 0,\ g_i > 0, g_U = 0\} \tag{11}$$

Let us us define the polyhedral cone of *semipositive subconservation relations* associated with metabolic network S with irreversible reactions T as:

$$G_s = \{g \in \mathbb{R}^m \mid g^T S_T \leq 0,\ g^T S_{N \setminus T} = 0,\ g \geq 0\}. \tag{12}$$

Let E_s be the extreme rays of G_s, then the emptiness of the set in Eq. 11 is equivalent to:

$$P_i(E_s) \subseteq P_U(E_s). \tag{13}$$

Given E_s, the set of *extreme semipositive subconservation relations*, Eq. 13 forms a necessary and sufficient condition for producibility in the context of thermodynamic constraints.