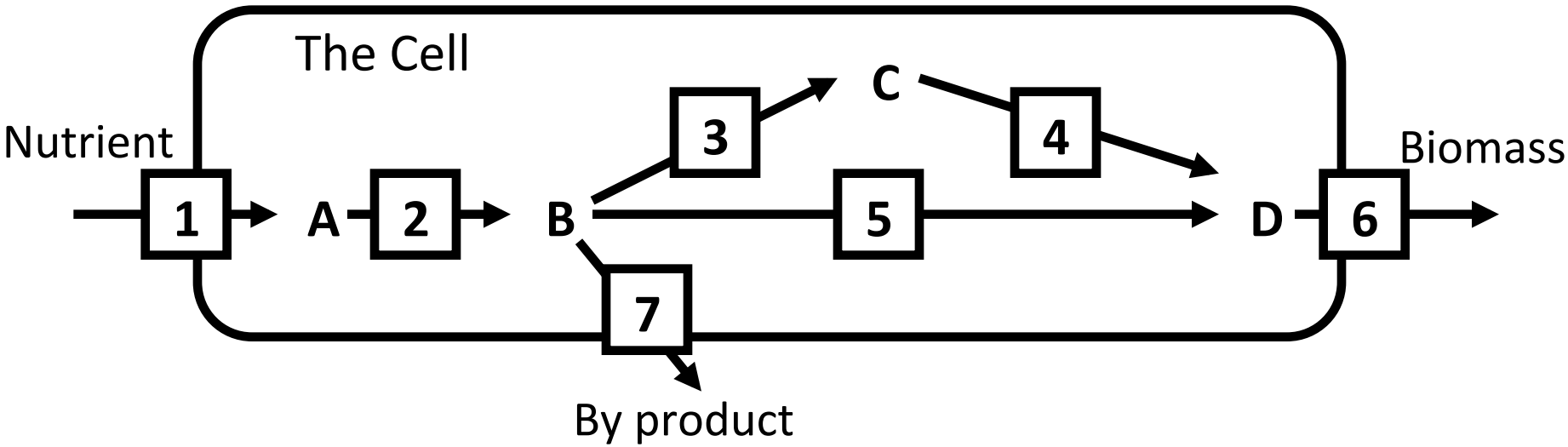
PlantSEED Workshop: Introduction to Metabolic Modeling

Presented by Christopher Henry

Flux Balance Analysis



Assuming Steady State:

No internal metabolite is allowed to accumulate

Thus, reaction rates are constrained by mass balances

For example:

At Steady State:

$v_1 = v_2$

$v_2 = v_3 + v_5 + v_7$

$v_3 = v_4$

$v_4 + v_5 = v_6$

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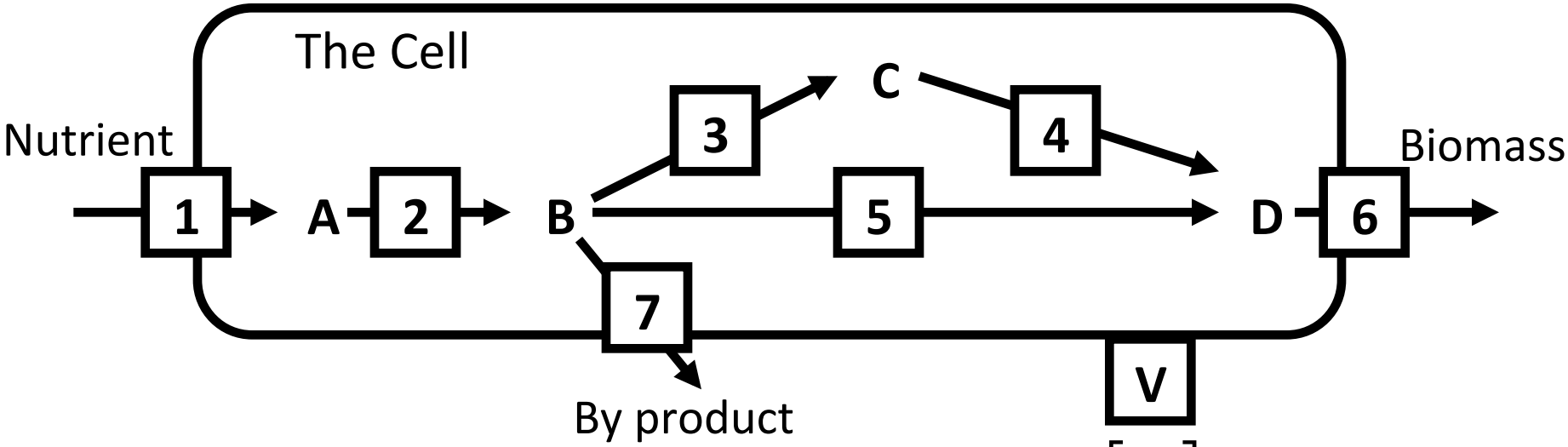
Flux Balance Analysis



$$
\begin{array}{c} \\ A \\ B \\ C \\ D \end{array}
\begin{array}{c}
\begin{array}{ccccccc} \boxed{1} & \boxed{2} & \boxed{3} & \boxed{4} & \boxed{5} & \boxed{6} & \boxed{7} \end{array} \\
\begin{bmatrix} 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & -1 & 0 & -1 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & -1 & 0 \end{bmatrix}
\end{array}
\bullet
\begin{array}{c} \boxed{V} \\ \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ \boxed{v_6} \\ v_7 \end{bmatrix} \end{array}
=
\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}
$$

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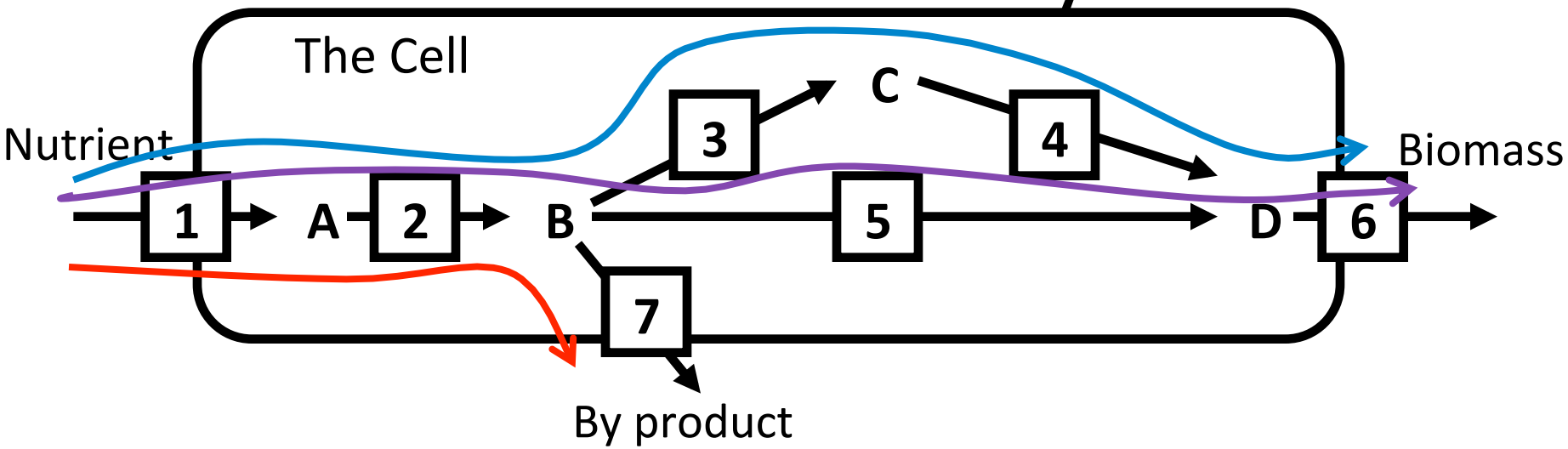
Flux Balance Analysis



- Now we have an underdetermined system
- There are three completely independent and equally valid solutions, with infinite combinations
- How can we tell which one is correct?
    - More measurements
    - Predict the correct solution using an objective function (e.g. growth)

Shape of FBA Solution Space

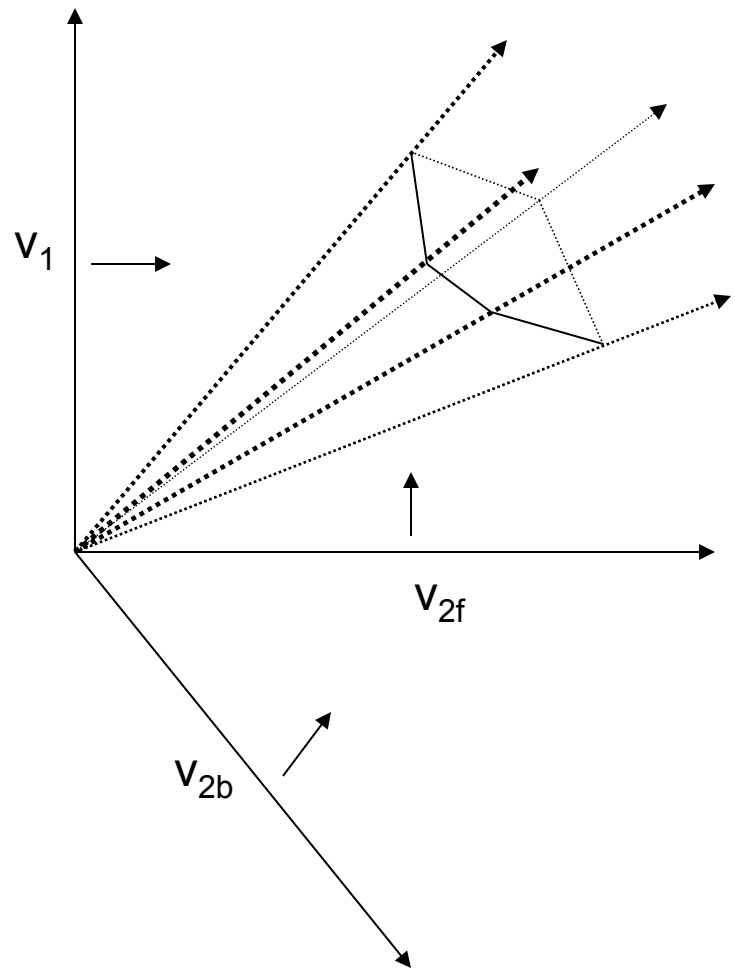
In reality, metabolic models are more complex, with infinite possible solutions

The steady-state solution space falls within a convex cone emerging from the origin of the reaction rate parameter space.

Optimization is used to select a subset of this space as the most "biologically relevant"

Optimization of biomass production is the most common criteria

How do we characterize the flux solution space?



Characterizing Reactions with Flux variability analysis (FVA)

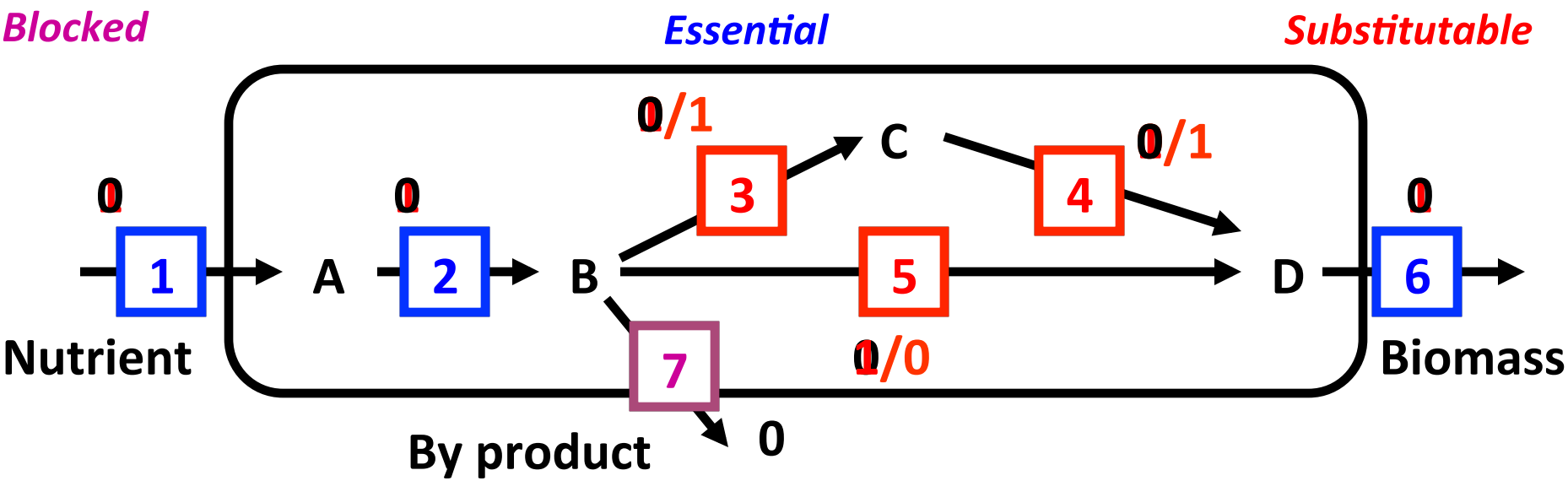
-Maximizing yield to biomass from nutrient

-Minimize and maximize each individual reaction

-7 is used in no solutions because it reduces yield to biomass (*blocked*)

-1,2, and 6 are used in all solutions because it is needed to produce and transport nutrient, and biomass (*essential*)

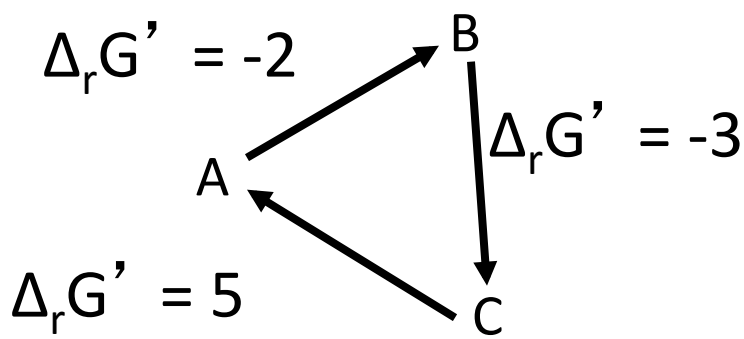
-[3,4], and 5 are used in some solutions, but are not necessary (*substitutable*)



Thermodynamically Infeasible Flux Loops

-Very often flux through some reactions is completely unconstrained, varying all the way between the upper and lower bounds

-Such reactions are involved in thermodynamically infeasible flux loops such as:



-We minimize the sum of fluxes in our FBA to eliminate flux through these loops

PlantSEED FBA Process

1.) Maximize the primary objective function (biomass by default)

2.) Fix objective at maximum value, and then minimize the sum of all fluxes

3.) Next, fix objective at 10% of optimal value, and then minimize and maximize each individual reaction to conduct FVA

4.) Save solutions to PlantSEED workspace