

im working on a metabolic modelling assignment, were I performed FVA. In FVA, we loop over every reaction of interest and once maximize and once minimize its flux via FBA; thus obtaining the permissible flux range for each reaction in the model. This is one of the questions: Identify any reactions with gene expression-imposed maximal reaction activities, whose permissible flux range in forward direction is nonzero yet comes out less than its upper flux bound. Explain why a set of reactions behaves this way. [15 pt].

Got it! Let's break this down carefully. You're dealing with **Flux Variability Analysis (FVA)**, and the question is about reactions whose **permissible flux ranges are constrained by gene expression**, but the FVA results show that the **maximum flux achievable is less than the theoretical upper bound**. Here's a step-by-step explanation:

1. Key concepts

- **FVA:** For a given reaction, FVA computes the **minimum and maximum fluxes** that the reaction can take while still allowing the network to achieve its optimal objective (e.g., biomass production).
- **Upper flux bound (UB):** The maximal allowed flux for a reaction, often imposed by reaction constraints, enzyme capacities, or gene expression data.
- **Gene expression-imposed maximal reaction activity:** If you have integrated transcriptomics/proteomics, you may limit certain reactions based on enzyme abundance or expression levels (GPR constraints).

2. Scenario in the question

The reaction satisfies all of these:

1. **Gene expression imposes a maximum flux**, so there is a UB on the reaction.

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2. Scenario in the question

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2.

FVA shows a nonzero flux range in the forward direction, i.e., the reaction can carry flux.

3.

FVA maximum flux < upper bound, i.e., the network cannot push the reaction all the way to its maximum allowed by gene expression.

3. Why does this happen?

This happens due to **network-level constraints**. Even if the reaction could theoretically carry a higher flux according to gene expression or thermodynamics, the **network stoichiometry and interactions with other reactions limit it**.

Main reasons:

1. Stoichiometric coupling:

- Some reactions are connected to others in such a way that they can only carry a certain flux without violating mass balance.
- Example: If a reaction produces a metabolite that is consumed slowly downstream, its flux is limited by the downstream reactions.

2.

Objective function constraints:

- FVA maximizes or minimizes each reaction **without changing the optimal objective flux** (like biomass).
- A reaction might not need to reach its upper bound to satisfy the network objective, so FVA gives a max less than the UB.

3.

Competing pathways:

- Multiple reactions can achieve the same metabolic function. Flux may be distributed among them, so no single reaction reaches its UB.

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4.

Thermodynamic or directionality constraints:

- Even if the UB allows a high forward flux, the actual network constraints might make full forward flux infeasible without violating mass balance.

4. Summary explanation you can write

Certain reactions in the model show FVA-permissible maximum fluxes that are less than their gene-expression-imposed upper bounds because the **network-level stoichiometry, competing pathways, and the requirement to maintain optimal objective flux** restrict the flux distribution. Even though the reaction could theoretically operate at a higher rate, the rest of the metabolic network imposes constraints that prevent it from reaching its upper bound. This is a common outcome in FVA for reactions that are part of tightly coupled pathways or redundant alternative pathways.

If you want, I can also **give a concise example** showing this with a small toy metabolic network—it usually makes this explanation much clearer in assignments.

Do you want me to do that?



explain why a set of reactions has a positive minimal flux in the FVA?

Great question — this is actually a very important concept in interpreting FVA results.



When you see a **positive minimal flux** (i.e., FVA minimum > 0) for a reaction, it means:

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Great question — this is actually a very important concept in interpreting FVA results.

When you see a **positive minimal flux** (i.e., FVA minimum > 0) for a reaction, it means:

1. What a positive minimal flux means

- The reaction **must** carry some flux in the forward direction in order for the network to achieve the chosen objective (e.g., biomass, ATP production).
- In other words, the network cannot find a feasible flux distribution with this reaction completely shut off (flux = 0) while still reaching the same optimal objective value.

So this is identifying **essential reactions** under the given growth/environmental condition — they are "forced on" by the network.

2. Why this happens

There are several network-based reasons:

1. Stoichiometric necessity

- The reaction produces a metabolite that is essential for biomass precursors or energy.
- Without it, mass balance would be violated or biomass could not be synthesized.

2. No alternative pathways

- There is no other reaction or pathway that can perform the same conversion.
- Hence, the network is "locked" into using this reaction.

3. Coupling relationships

- Some reactions are **fully coupled** to the objective function or to other reactions (e.g., glycolysis steps under certain media conditions).
- If one carries flux, the others must carry a proportional amount, which gives them a strictly positive minimum flux.



4. Model objective requirement

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4. Model objective requirement

- Because FVA holds the **objective flux at its optimal value**, the solution space is restricted to those that achieve max growth/ATP/etc.
- This often forces certain fluxes to be strictly positive — otherwise the objective cannot stay optimal.

3. Biological interpretation

- Reactions with **positive minimal flux** are **essential for the cell's growth in the simulated condition**.
- This can be used to identify **conditionally essential genes or drug targets**, since their flux cannot be turned off without compromising growth.

4. Example (conceptual)

Imagine a very small network:

nglnx


Glucose uptake → Glycolysis → Pyruvate → Biomass

Code kopiëren

If there is only one glycolysis reaction, FVA will show:

- **Min flux > 0** for glycolysis, because biomass cannot be made without pyruvate, which only comes from this reaction.
- Shutting it off would make growth impossible, so its minimum flux is forced to be positive.

Summary you could write in your assignment

A set of reactions has a positive minimal flux in FVA because they are **stoichiometrically and functionally essential** for maintaining the optimal objective flux (e.g., growth rate) under the given conditions. Their activity is required to supply essential precursors or energy, and there are no alternative pathways that could bypass them. Consequently, even when minimizing their flux, the network cannot set them to zero without reducing  the objective, resulting in a strictly positive minimal flux.

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A set of reactions has a positive minimal flux in FVA because they are **stoichiometrically and functionally essential** for maintaining the optimal objective flux (e.g., growth rate) under the given conditions. Their activity is required to supply essential precursors or energy, and there are no alternative pathways that could bypass them. Consequently, even when minimizing their flux, the network cannot set them to zero without reducing the objective, resulting in a strictly positive minimal flux.

Would you like me to also explain **the difference between a positive minimal flux vs. a positive maximal flux (but zero minimum)**? This often comes up when interpreting FVA results side-by-side.

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