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NetCoupler: Inferring causal pathways between high-dimensional metabolic data and external factors

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Background: Metabolic data, especially from -omics, is challenging to meaningfully analyze and visualize. Even more so when we're interested in potential causal pathways. Our **aim** is to develop an algorithm and R package to estimate and visualize these pathways, in order to be used by the wider research community.

Methods: The NetCoupler algorithm estimates causal pathways between a network of metabolic variables and either 1) an "outcome" variable (i.e. influenced by the network), 2) an "exposure" variable (i.e. influences the network), or 3) both. The R package is being developed at github.com/NetCoupler and aims to be user-friendly.

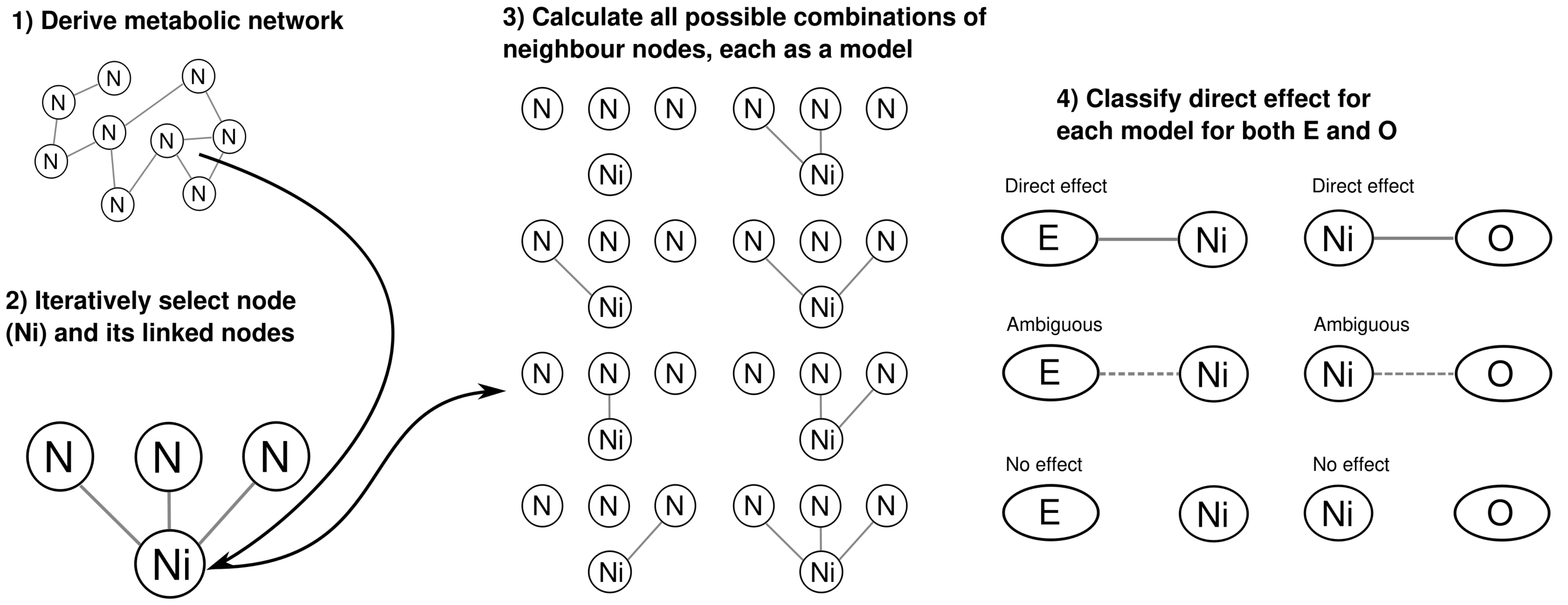
The algorithm implementation follows these steps, visually shown in Figure 1:

1. The network skeleton of metabolic variables is constructed
2. Each node in the network is selected
3. All combinations of neighbours connected to the node are formed and used for adjustment in subsequent models
4. Multi-model estimation occurs and links are classified as either no effect, ambiguous, or as direct effects based on model estimates

Example of an analysis on the UK Biobank dataset using this algorithm is shown in Figure 2.

Conclusion: We hope the NetCoupler package will give researchers more tools to meaningfully analyze complex -omic style data.

Figure 1: NetCoupler algorithm (R package at github.com/NetCoupler) process, identifies potential pathways between exposure (E), metabolic network (N), and outcome (O)



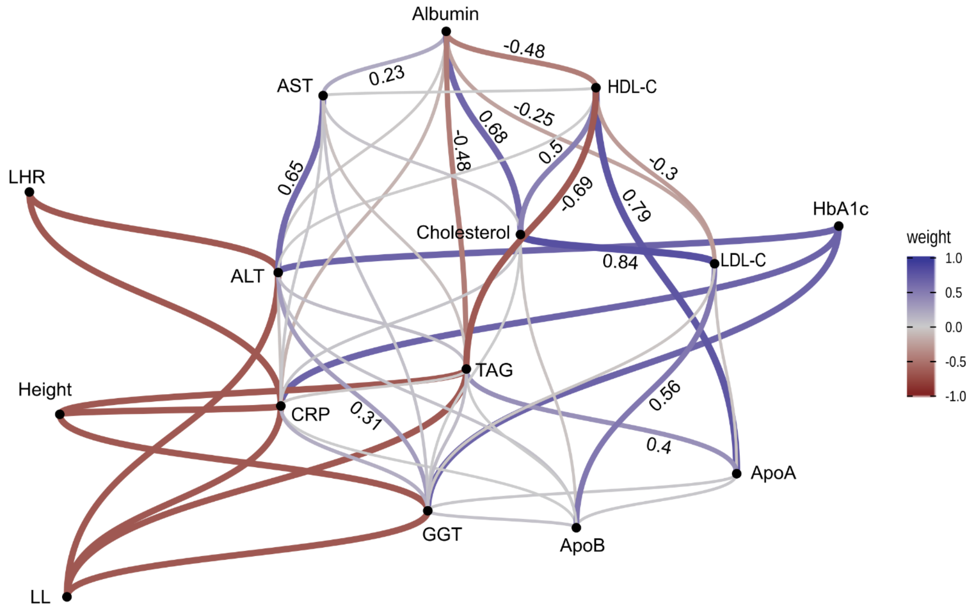
1) Derive metabolic network

2) Iteratively select node (Ni) and its linked nodes

3) Calculate all possible combinations of neighbour nodes, each as a model

4) Classify direct effect for each model for both E and O

Figure 2: Example analysis of NetCoupler identifying pathways between stature (marker of early growth), network, and HbA1c in the UK Biobank



Potential pathways identified from the NetCoupler algorithm. A darker blue link indicates a positive relationship, while a darker red one indicates a negative relationship. Grey lines between metabolic variables are the derived neighbours, but with weaker connections. Numbers between metabolic variables indicate the weights for the strong links (a larger number suggests a stronger link). Links shown with the stature or HbA1c variables and the network variables were classified as direct effect links; while all other connections with metabolic variables had been classified as ambiguous, they were removed for better visual presentation.