

# Predicting Nash equilibria for microbial metabolic interactions

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## Background

Microbial metabolic interactions impact ecosystems, human health and biotechnological processes profoundly. However, their determination, which is important to related bio-design purposes, remains elusive, invoking an urgent need for predictive models that seamlessly integrate ecological, evolutionary principles and metabolic details.

## Results

Recognizing that metabolic interactions form a complex game in which an individual's strategies is a metabolic flux space constrained also by other individuals' strategies, we formulated a bi-level optimization framework termed NECom for prediction of Nash equilibria of microbial metabolic interactions. We successfully predicted several classical games in the context of metabolic interactions that were falsely or incompletely predicted by existing methods. A reported algae-yeast co-culture system that shares typical cross-feeding features of lichen, a model system of mutualism, has been analyzed using NECom, 488 growth conditions corresponding to 3,221 experimental data points were simulated. Without training any parameters using the data, NECom is more predictive of species' growth rates given uptake rates compared with flux balance analysis with an overall 63.5% and 81.7% reduction in root-mean-square error for the two species. The improved capability originates from the novel formulation to get rid of the 'forced altruism' hidden in previous static algorithms while allowing for sensing all potential metabolite exchanges and responding accordingly between microbial members, which is a feature missing in dynamic methods.

## Methods

The biggest advance of NECom reported here is free of 'forced altruism' setup. While the inner problem is essentially the Flux Balance Analysis (FBA) problem, the primary innovation lies in modeling how community metabolites available to the member microbes depend on the exchange profile (strategy) of each microbe, as shown in the schematic diagram in Fig.1

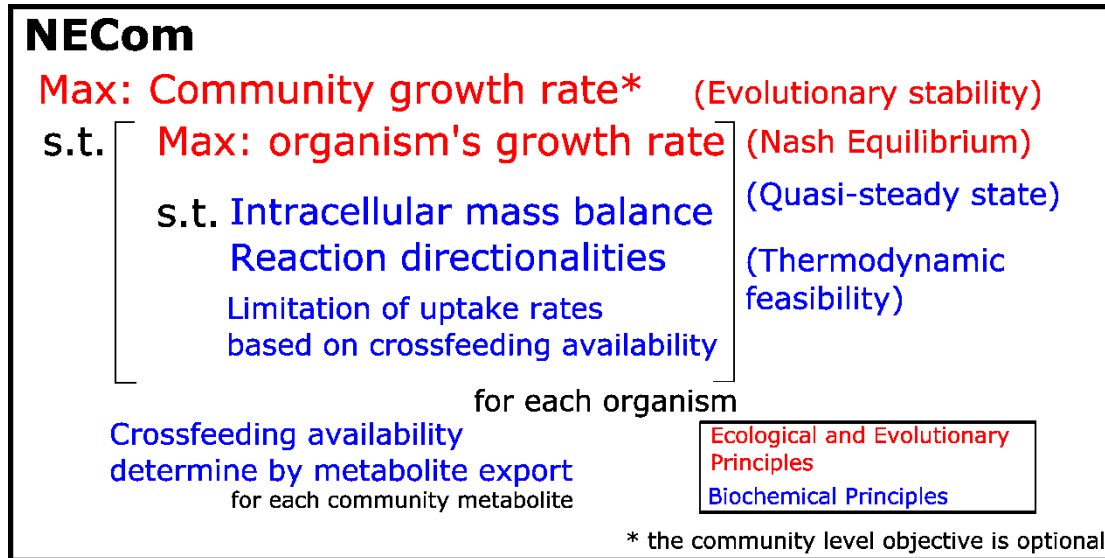


Fig.1 Schematic diagram of the NECom formulation.

Crossfeeding availability of each community metabolite is determined by metabolite export can be expressed mathematically as follow,

$$X_n v_{j,n}^{ut} \leq \max \left\{ \sum_{k \in N, k \neq n} X_k v_{j,n}^{com}, 0 \right\} \quad \forall n \in N$$

Where  $N$  is the set of organisms in a community, The community exchange flux  $v_{j,n}^{com}$  is bounded by the net community exchange fluxes by other members, and normalized by the relative abundance  $X_n$  in eq. (5). By bounding only the uptake flux, no export is forced by the need of other members. The max function is necessary if a member is exporting a metabolite and the net exchange by the rest of the community can be negative.

## Conclusion

We developed a novel bilevel framework termed ‘NECom’ that is able to preserve autonomy of each community member in environmental conditions shaped by other species, thus ensuring this algorithm free of a long hidden ‘forced altruism’ setup in previous static algorithm while allowing for ‘sensing and responding’ between microbial members that is missing in dynamic methods. With genome scale metabolic models and minimal input (media condition), NECom is able to predict microbial phenotypes at Nash equilibria by searching within the continuous strategy space. The results have been validated by traditional game theoretical analysis and large-scale data from a well-documented co-culture system (i.e yeast-algae). Significant improvement in prediction compared with commonly used joint-FBA and DMMM has been demonstrated. A major limitation of NECom is the computational complexity since it involves solving mixed integer non-linear programming problems. We envision that by developing approximation algorithms and incorporating NECom into dynamic frameworks will overcome this limitation.