Predicting Nash Equilibria for Microbial Metabolic Interactions

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https://youtu.be/mFTwyAv3ch4

Introduction

Microbial metabolic interactions impact ecosystems, human health and biotechnology profoundly. However, their determination, important to relative bio-sign purposes, remains elusive, invoking an urgent need for predictive models seamlessly integrating metabolism with evolutionary principles that shape community interactions.

Inspired by the evolutionary game theory, we formulated a bi-level optimization framework termed NECom for which any feasible solutions are Nash equilibria of microbial community metabolic models without the necessity to invoke a community-level objective function. Distinct from the discrete payoff matrix approach, NECom models the continuous interdependent strategy space of metabolic fluxes.



NECom is free of 'Forced Altruism' setup

A problem hidden In previous algorithms (e.g. Joint FBA, OptCom) for predicting microbial community metabolic phenotypes is forced altruism, which force individual organisms to produce a certain amount of metabolites for other members prior to optimizing its own fitness whenever doing so maximizes the community-level objective function value. The applicability of 'forced altruism' should be



altruism' Fig.1 Schematic diagram of the NECom formulation.

questioned for microbes separate from each other by cell envelopes and no controlled by regulatory mechanisms (e.g., host-regulation, quorum sensing, etc.).

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

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NECom significantly improves prediction accuracy

We analyzed a reported algae-yeast co-culture system that shares typical crossfeeding features of lichen, a model system of mutualism. 488 growth conditions corresponding to 3,221 experimental data points were simulated. Growth rates were predicted using both NECom and Joint-FBA. The average root mean squared error (RMSE) for predicting the growth of C. reinhardtii and S. cerevisiae by NECom achieves a significant reduction of 63.5% and 81.7% compared to the predictions by Joint-FBA (Fig2. b). The errors of Joint-FBA predictions are majorly caused by 'forced altruistic' constraints, which force the C. reinhardtii model using photons to convert low energy carbon containing metabolites (primarily) released by S. cerevisiae to various energy richer substrates subsequently to be consumed by S. cerevisiae (Fig. 2c)



Fig. 2 (a) Uptake and growth rates estimated from the data. (b) Validation and predictions: Example predictions by NECom and Joint-FBA, respectively. Prediction of growth rates under the same uptake condition with varying relative abundance of organisms. (c) Difference of predicted cross-feeding fluxes between NECom and Joint-FBA.

NECom predicting Nash Equilibrium verified by traditional matrix analysis

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. 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 welldocumented co-culture system (i.e. yeast-algae). Significant improvement in prediction expressed with exemption using the been demonstrated



Fig.3. A case consists of two members, both capable of producing biomass precursors A and B, but at different ATP costs. The strategy transition path to determine NE through payooff matrix analysis is illustrated in the right side

Conclusion

- A new optimization algorithm called 'NECom' is formulated to find Nash equilibria of microbial community metabolic networks. The algorithm always returns Nash Equilibria as solutions regarless of the optimization objective function due to a novel formulation in the constraints to avoid 'forced altruism' that has been observed in previous static algorithms as well as to search the entire solution space by looking at all potential metabolic interactions at the same time that previous dynamic algorithms do not consider.

 NECom is tested against previous algorithms and successfully predicts solutions consistent with evolutionary game theory in metabolic toy models correponding to both prisoner dilemma and cooperation.

both prisoner dilemma and cooperation . - NECom is applied to an experimental dataset of yeast-algae growth on various carbon and nitrogen availability and shows more accurate predictions than the direct extension of flux balance analysis (FBA)

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