Cross-feeding percolation phase transitions of inter-cellular metabolic networks

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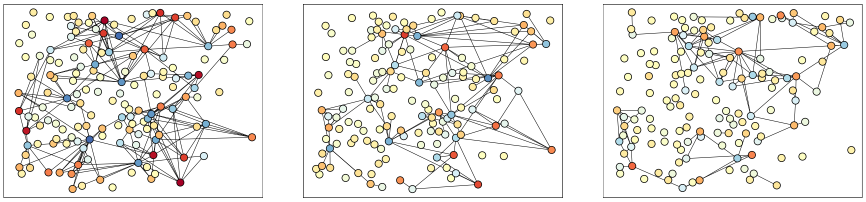
Intercellular exchange networks are essential for cellular populations to adapt, supporting processes ranging from information processing to shaping micro-environments. While diffusional exchanges have traditionally been difficult to quantify, recent advances in nanotechnology now enable precise probing of the dynamic unfolding of such networks [1]. In this study, we introduce a tiling-based method to reconstruct intercellular exchange networks from high resolution flux data, focusing on how individual cells within a mixed population exchange metabolites. We apply this approach to a mammalian co-culture system where lactate exchanges regulate overflow acidification. Initially, the network exhibits a dense web of exchanges that progressively fragments over time, leaving behind small, isolated motifs. We explain these observations, with a two-parameter Maximum Entropy multicellular metabolic model that incorporates diffusion-driven exchanges through a set of global constraints linking cellular behaviors. The model predicts a transition from a densely interconnected network to a sparse, motif-dominated state as glucose and oxygen consumption levels shift. We numerically characterize this crossover, revealing a power-law decay in the cluster-size distribution at the critical transition, and analytically derive the critical line using a mean-field approximation based on percolation theory. By comparing empirical data with theoretical predictions, we find that cellular populations evolve by remaining near the crossover point between these two regimes. These findings offer new insights into the collective behaviors that drive the adaptive dynamics of cell populations [2].



Snapshots of the experimental system at different times, increasing from left to right. Lines represent intercellular exchange of acids. Note that the network becomes sparser as cells adapt to the medium.

References

[1] V. Onesto, S. Forciniti, F. Alemanno, K. Narayanankutty, A. Chandra, S. Prasad, A. Azzariti, G. Gigli, A. Barra, A. De Martino, et al. *Probing Single-Cell Fermentation Fluxes and Exchange Networks via pH-Sensing Hybrid Nanofibers* ACS Nano **17**, 3313 (2023).
[2] Latoski, L. C. F., De Martino, D., De Martino, A. *Cross-feeding percolation phase transitions of inter-cellular metabolic networks* (In production)

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