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Karyotype heterogeneity driving evolutionary adaptation: from experiments to theory



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Errors in mitosis underlie chromosome instability (CIN), generating aneuploid cells with diverse chromosome stoichiometry (referred hereafter as karyotype). The resulting DNA dosage imbalance leads to genome-wide changes in RNA and protein expression on multiple levels. Our recent work has shown that the basal mitotic error rate is not minimized for euploid yeast growing under the optimal condition. Further, this rate can be drastically enhanced under different stress conditions, producing karyotypically heterogeneous cell populations. By growing a cohort of aneuploid strains with diverse karyotypes under a wide range of stress conditions, we found that the degree of selectable phenotypic variation, the basis of evolvability, increases linearly with increasing stress magnitude. We developed a general theoretical framework to explore this relationship by abstracting the heterogeneous population to a match/mismatch with external conditions within a multidimensional feature space. The experimentally observed relationship can be predicted with both numerical simulations and the analytical result of the model. Surprisingly, the model shows that that evolvability of the heterogeneous population is dependent on the system's inherent robustness, establishing a mathematical linkage between these two seemingly contradicting properties of biological systems. We further applied our model to the published pharmacogenomics data of breast cancer cell lines. This analysis revealed a similar stress-evolvability relationship in cancer cells as that observed in yeast and illuminated a mathematical means for identifying cancer cell lines that may help understand "multi-drug-tolerant persisters" or "cancer-initiating cells".