

***A new phenotyping paradigm for understanding  
the functional genomics of yeasts***

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Single-channel optical density measurements of population growth in solution or as colonies on plates have become the favorite large scale methodology for bridging the gene-function gap in biological model organisms such as yeast. However, it is becoming increasingly clear that a substantial amount of the observed genetic variation does not leave any imprint on growth under standard laboratory conditions because of low data dimensionality. The bulk of this cryptic genetic variation has undoubtedly been subjected to adaptive evolution and we can be quite confident that it is functionally relevant. Hence, more refined biochemical investigations should be able to reveal information at deeper biochemical levels that although evolutionary marginal may represent distinct functional signatures. In this paper we introduce a protocol for high-throughput Fourier transform infrared spectroscopy (FTIR) measuring chemical fingerprints of metabolic products of yeast deletion strains. The protocol includes high-throughput cultivation for FTIR spectroscopy, FTIR measurements and spectral pre-treatment to increase measurement accuracy. We demonstrate the applicability of this approach by determining the FTIR signatures of all viable *Saccharomyces cerevisiae* gene knockouts of genes known to be involved in lipid biosynthesis. Despite showing no detectable growth aberrations during standard laboratory conditions many of the examined knockouts featured characteristic and highly reproducible FTIR phenotypes over the whole spectral range. GC-MS analyses of lipid content confirmed deviations in lipid profiles for strains with aberrant FTIR phenotypes. The spectral data could be causally interpreted with reference to our current understanding of fatty acid metabolism. Our results show the potential of large scale FTIR phenotyping in the detection and interpretation of subtle biochemical effects of genetic variation that is not reflected in growth aberrations.