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Comment on ''Mathematical modeling of unicellular microalgae and cyanobacteria metabolism for biofuel production'' by Baroukh *et al*. [Curr Opin Biotechnol. 2015, 33:198–205]☆

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This letter concerns an article recently published in '*Current Opinion in Biotechnology* by Baroukh *et al*. [1]'. The issue we wish to bring to light is the authors' claim that dynamic metabolic models including Hybrid Cybernetic Model (HCM) [2,3] and Lumped HCM (L-HCM) [4,5] are based on the balanced growth hypothesis so that they are unable to simulate the accumulation of intracellular metabolites. This is a misrepresentation of these models due to the following reasons.

First, the HCM and L-HCM assume the quasi-static state of intracellular variables, but not balanced growth. They are not equivalent concepts. Balanced growth is often used to denote log (or exponential) growth phase (in a bath reactor), during which specific growth rate and relative flux distribution (thus, biomass composition as well) remain the same. To get a precise mathematical understanding of balanced growth, we cite Fredrickson *et al*. [6]. In contrast, the quasi steady-state approximation implies that the concentrations of intracellular metabolites instantaneously arrive at a steady state to be balanced with dynamically changing exchange fluxes (such as substrate uptake rates). The falsity of equating quasi-static growth to balanced growth becomes patently obvious when uptake fluxes undergo significant changes (e.g., from famine to feast conditions), as it leads to notably different metabolic states (such as flux distribution and cellular composition). Simulation of such dynamic metabolic shifts is the key capability of HCM and L-HCM, neither of which have anything to do with balanced growth. Insofar as dynamic flux balance analysis [7] depends on variable uptake rates, this approach can also not be regarded as dealing with balanced growth.

Second, as demonstrated previously, the HCM and L-HCM can accommodate the accumulation of intracellular metabolites (particularly, metabolites with slow dynamics such as carbon and nitrogen storage molecules), by treating them as extracellular variables (in computing elementary modes) without admitting the assumption of quasi-static state [8]. In our past publications, we have continued highlighting the necessity of accounting for slow dynamics of some of the intracellular metabolites [9,10]. In this regard, we are not convinced by the authors' claim that the ability of their framework termed DRUM [11] to account for the accumulation of intracellular metabolites is fundamentally new. Notably, our paper [8] on the same was not cited.

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In order to provide the community with accurate information on dynamic metabolic models that are based on quasi steady state approximation, we feel it behooves the authors to correct the false statements in their paper.

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