C M D B

Biomanufacturing, particularly to produce biologic pharmaceuticals, has entered an era of intensiýed processing in which mammalian cells are cultivated to very high cell densities and with very high product titers (*i.e.*, higher drug concentrations in the cell-free culture broth). This allows the use of smaller, cheaper bioreactors and lowers puriýcation costs.

A critical requirement for keeping cells at these high densities and producing high product levels is having high nutrient concentrations in media and in feed streams, particularly amino acids, salts, and sugars. Often, the optimal media for a particular cell culture has concentrations of some species (usually amino acids) that are close to or above their pure component solubilities in water. Because media formulations often have twenty (or even a hundred) components, knowing the solubilities of all the components in these complex mixtures can be a problem. Without this understanding, formulating stable multi-component media is difýcult, posing a signiýcant challenge to process design and scale-up. Media formulations have relied on extensive trial-and-error experiments that cause bottlenecks in biomanufacturing process development.

A phase-equilibrium model that can predict solubilities in such systems could provide an efýcient path to media formulation. Modeling these multi-component solutions requires knowledge of all the different intermolecular interactions and their impacts on solubility. For media, these interactions include (at a minimum) dispersion forces, ionic forces, and the effects of the formation of strong chemical complexes. For example, a solution of one amino acid (AA) with one salt (XY) in water can have nine or more different species present in solution, including the neutral AA, the AA zwitterion, AA^+ or AA^- (depending on the pH), molecular XY, X^+, Y^-