this continuous feeding strategy for mammalian cell cultures relies on equipment feedback control, which can introduce variability into a feeding process.

Summarily, a drawback common to all of these methods is the fact that they all rely on some sort of instrument-obtained feedback in order to manage the process. What is needed, therefore, is a method of feeding a cell culture that can be tailored to the specific needs of a given cell culture, can be automated and does not rely on instrument-mediated feedback to control the nutrients delivered to the cell culture.

SUMMARY ~~OF THE INVENTION~~

In one aspect, there is provided a method of continuously feeding a mammalian cell culture that does not employ feedback control, comprising:

(a) providing a vessel comprising a mammalian cell culture comprising mammalian cells and media;

(b) determining preferred values for the consumption rate (K_1) of a nutrient, growth rate (K_{21}) and growth rate (K_{22}) of the cell culture;

(c) providing an apparatus adapted to impart a continuous feed stream to the cell culture, wherein the apparatus comprises a controller module adapted to continuously feed the culture at a flow rate F, wherein

F is defined as $K_1 \exp(K_{21}t^2 + K_{22}t)$;

t is the duration of time from the time the feed stream is added to the bioreactor to the time when the feed stream is stopped; and

K_1, K_{21} and K_{22} are the values determined in (b); and

(d) activating the controller module to initiate continuous feeding of the cell culture.

A method of continuously feeding a mammalian cell culture that does not employ feedback control is provided. In one ~~embodiment~~example the method comprises (a) providing a vessel comprising a mammalian cell culture comprising mammalian cells and media; (b)

determining preferred values for the consumption rate (K_1) of a nutrient, growth rate (K_{21}) and growth rate (K_{22}) of the cell culture; (c) providing an apparatus adapted to impart a continuous feed stream to the cell culture, wherein the apparatus comprises a controller module adapted to continuously feed the culture at a flow rate F, wherein F is defined as $K_1\exp(K_{21}t^2 + K_{22}t)$; t is the duration of time from the time the feed stream is added to the bioreactor to the time when the feed stream is stopped; and K_1, K_{21} and K_{22} are the values determined in (b); and (d) activating the controller module to initiate continuous feeding of the cell culture. In one ~~embodiment~~example K_1, K_{21} and K_{22} are empirically determined. In another ~~embodiment~~example K_1, K_{21} and K_{22} are modeled. In a further ~~embodiment~~example the controller module comprises a computer. In still another ~~embodiment~~example the feed stream comprises multiple nutrients. In a further ~~embodiment~~example the osmolality of the cell culture remains constant throughout the method. In another ~~embodiment~~example the nutrient fed to the culture is glucose. In other ~~embodiments~~examples the mammalian cell culture is a CHO cell culture. In a further ~~embodiment~~example the controller module is activated in response to a preselected lactate level in the cell culture, while in another ~~embodiment~~example the controller module is activated in response to a preselected glucose level in the cell culture. In yet another ~~embodiment~~example the controller module is activated in response to a preselected level of an amino acid, such as asparagines or glutamine. In still a further ~~embodiment~~example the feed stream comprises two or more nutrients.