SIMBIOS - A New Simulation Program for Biotechnology with Novel Design*

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Process simulation is a viable tool for chemical engineering process design. A large number of process simulation programs have been developed to this end, like ASPEN, PROCESS, HYSIM, just to mention a few widely known brand names. However, most of these programs have been developed to meet the needs of chemical process engineers, one notable exception being Bioprocess Simulator of ASPEN.

SIMBIOS is a new program package currently under development by a Hungarian and Austrian team which is specially designed to meet requirements of bioprocess simulation. Besides offering models for most unit operations in use in bioprocess engineering, a specially developed structure ensures optimal applicability for bioprocess simulation.

SIMBIOS will run on IBM compatible PC's. It will be available in a first version by June 1993. This paper intends to give the outline of program architecture and some preliminary informations on this program package.

Key words:
Simulation program, bioprocess, simulation

Introduction

Process technologies are in fast development. A host of new requirements have occupied the center stage of interest of the process engineer. Most notable among them are ecologic requirements which have changed the very nature of process development. They call for cleaner production and optimized use of raw materials as well as energy sources, thus minimizing waste streams.

The task process engineers are facing to meet these requirements as well as the requirement of economic efficiency is a systemic process optimization during the development of a process[1]. This calls for the use of simulation techniques throughout the whole design process. This calls for the use of simulation techniques throughout the whole design process.

Flow sheet simulation has not gained the same status of a widely used process development tool in biotechnology, so far. One reasons for this is that biotechnologic process development has usually been carried out in a more empirical way than chemical engineering design. A second reason is that bioprocesses are supposed to be too complex for simulation programs solely based on literature data.

A recent study[2], however, showed that results of a bakers yeast process based on models and data from literature compares very well with empirical data from runs in an industrial size plant, even at very different operating conditions. This means, that models for bioprocesses have already matured to a level which allows simulation in basic engineering. The development of special biotechnology flow sheet programs, however, is only suitable if bioprocess engineers really gain substantially in using them.

There are mainly two advantages in using a flow sheet program in biotechnology:

a) Higher economic and ecologic efficiency of the resulting design

b) Faster process development on the base of fewer empirical data.

ad a) Bioprocesses are in almost all cases less economically efficient than chemical engineering if it comes to producing bulk chemicals. This is, of course, to be attributed to a large extend to high costs of raw materials and to inherent disadvantages, like low concentrations of products and catalyst and the predomination of water in process streams.

Contrary to common belief, bioprocesses are usually ecologically inefficient, too. Most biotechnological technologies for the production of staple products (like ethanol, bakers yeast and organic acids) are burdened with huge, heavily contaminated waste water streams. So the potential ecologic advantage of bioprocesses, which use renewable resources and operate under benign conditions is literally wasted.

Although simulation is not the only solution to these problems, better process optimization will play a prominent role in increasing the efficiency as in chemical processes.

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ad b)Process optimization is not so important for high-price-low volume products in which most biotechnology research is currently invested. For those products, usually the rate determining step in development is passing rigorous safety tests required before they can reach the market[3].

In this case simulation can help to optimize the process and indicate where experimental data are necessary in order to get a reliable process design.

These advantages of simulation of bioprocesses can only be realized, if a flowsheet program meets the special requirements of biotechnology.

Requirements for a bioprocess simulation program

Almost all flow sheet simulation programs have been developed for chemical and petrochemical processes. They are centered on thermophysical separation steps (e.g. distillation, extraction, etc.) and they are generally poor when it comes to the simulation of conversion steps and mechanical unit operations. Thus, they are only applicable to down stream process simulation and are usually not well suited to optimize the entire bioprocess.

Any program applicable for bioprocess simulation has to fulfill several requirements. These are:

– High efficiency in simulating biochemical reactors for conversions with complex kinetics combined with mass transfer problems (reactor centered simulation programs).

– Capability to handle processes combining batch, semi batch and continuous unit operations.

– Models for "non conventional" thermophysical unit operations (e.g. chromatography, batch distillation, etc.)

– Models for mechanical separation unit operations (e.g. sedimentation, filtration, centrifugation, grinding, etc.)

– Models to simulate "biochemical" unit operations (e.g. sterilization, cell disintegration, etc.)

Although it is possible to "convert" a chemical engineering flow sheet program to meet these requirements it seems worthwhile to create a new type of programs, which are already structured more appropriately for these tasks.

Program architecture of SIMBIOS

The idea behind the development of SIMBIOS was to create a fast and reliable simulation tool for bioprocess engineers, helping them in process development and basic engineering. In order to allow a great number of engineers to use the program, it is conceived to run on a PC.

SIMBIOS will basically be applicable for three tasks:

a) Approximative process simulation for process development.

b) In detail studies for complex unit operations.

c) Process basic design.

ad a) At the beginning of any process development, an engineer has to check the feasibility of the conceived process. Usually there is some knowledge of the performance of the individual steps in the process, but the interactions of those steps are unknown. SIMBIOS allows to simulate a process (and find an approximative process optimum) on the base of simple linearized models for the unit operations involved.

ad b) During process development certain unit operations will emerge as the critical points in the process. A process engineer wants to simulate these unit operations in considerable detail. SIMBIOS allows the engineer to simulate complex unit operations, including bioconversion steps in a "stand alone" mode, but retains the results for later use in process basic engineering.

ad c) At the last level of design simulation the engineer wants to simulate the whole process. SIMBIOS allows for simulation of the process, using whatever information is already available from the in-depth simulation of individual unit operations.

The structure of SIMBIOS can be seen from fig. 1. SIMBIOS is organized in four different levels. These are:

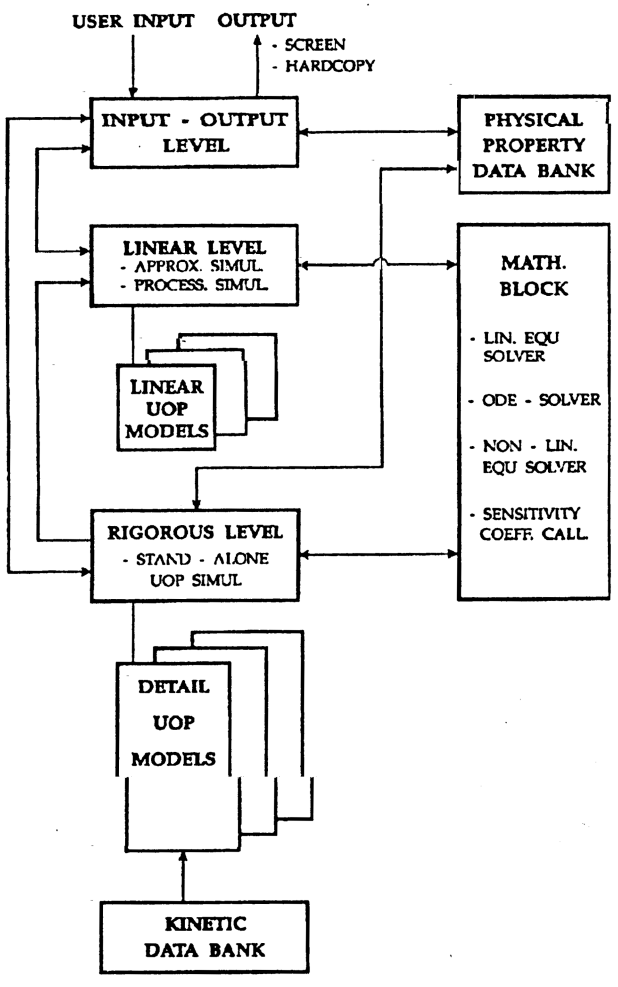

Fig. 1 – *Program architecture of SIMBIOS*

The input-output level:

This level has three tasks

- guiding the user through the input to the program via menus,
- data and file management, including retrieval of data stored in the physical properties and kinetic parameters data banks,
- creating the output of simulations results.

The linear level:

This level is responsible for approximative simulation as well as process simulation. It consists of linear models for each unit operation type covered by the program (see table 1).

Table 1 – *Unit operations covered by SIMBIOS*

Reactors:
Batch reactor
Semi-batch reactor
Continuous reactor
(all reactor units apply compartment mixing models and may be either aerobic or anaerobic)
Thermophysical Unit Operations
Distillation
Batch distillation
Liquid-liquid extraction
Chromatography
Mechanical Unit Operations
Filtration (crossflow, ultra filtration)
Sedimentation
Cyclones
Centrifugation
Biological Unit Operations
Sterilization
Cell disintegration
Auxiliaries
Heat exchangers (shell and tube, plate, condenser, evaporator)
Mixer/splitter
Pump
Compressor
Buffer tank

For approximative simulation, the user is asked to provide unit operation specific linearization parameters, coupling selected input with output variables. The program creates a system of sparse linear equations (up to 1 000). The solution of this system gives approximative mass balances for the process.

If the user wants to simulate the whole process using results obtained by in-depth simulation of individual unit operations (see below), SIMBIOS uses linearization parameters coupling all input to all output variables for the units already simulated in detail. These parameters, as well as the respective sensitivity coefficients, are calculated always when a unit is simulated in the rigorous level at certain (user supplied) values of the input variables (see below). The solution of the resulting linear equation system gives a good representation of the process as long as all input variables to the in-depth simulated units are close enough to those found by solving the linear equation system.

If some of those resulting values differ considerably from the user supplied guesses on which the simulation of individual unit operations was based, the user can either stop the calculation or continue an iteration until all flow variables between unit operations are reconciled. The user is supplied with the sensitivity coefficients for every output variable to every input variable for the units in question in order to help him to determine, if these differences are really bound to influence the overall simulation result.

On this level, the program also calculates necessary buffer tank volumes, if continuous units are connected to batch or semi batch units.

The rigorous level:

This level consists of a set of rigorous models for most unit operations included in the program. Every model is designed to act as a stand-alone simulation routine for the unit operation in question. The user has to supply values for the input variables and operation parameters. However, the former can also be obtained from an approximative simulation of the whole process.

With this input the routines calculate the output variables of the unit. They also calculate the sensitivity coefficients of the output variables with respect to the input variables at the given point of operation for later use in the process simulation task.

The mathematical block

All simulation routines (linearized level as well as rigorous level) transform the simulation task to a system of linear and non-linear equations, respectively a system of algebraic and ordinary differential equations. These equation systems are solved in the mathematical block. On top of this, symbolic derivatives of all equations are formed in the mathematical block, thus eliminating the necessity for time consuming numerical derivatives in the course of solving non-linear equation systems.

The solving capacity for the different mathematical tasks is:

- ODE mixed with algebraic equations: 200 equations, using ADAM's method in a program aquired via NETLIB based on[4].
- Sparse linear equation systems: 1 000 equations, using a modified GAUSS method.

The capacities mentioned above relate to a computer configuration consisting of a i386 processor (no coprocessor) with 32 MHz, 2MByte Ram and 40 MByte Winchester.

Future aspects

SIMBIOS will be available in mid-1993 in the form of a public domain version with limited capacity. The experiences of this edition will subsequently be used in an updated version with full capacity, available at the end of 1994.

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