AGRONOMIE

SPICE - a circuit simulation program for physiologists

P. CRUIZIAT & Randy THOMAS (*)

I.N.R.A., Laboratoire de Bioclimatologie, Domaine de Crouelle, F 63039 Clermont-Ferrand Cedex
(*) INSERM, U 192, Hôpital Necker, TT 6ᵉ étage, 149, rue de Sèvres, F 75015 Paris Cedex 15.

SUMMARY

This article presents a program named SPICE for simulation in plant physiology. It was originally developed to simulate electric and electronic circuits. For several years it has now been also used in various fields of human and animal physiology (classical physiology, membrane biophysics, pharmacokinetics...).
After a short description of SPICE's main features and capabilities, 3 simple illustrative examples are given : a whole plant water flow model, a coupling fluxes of water and solute across a membrane and a process obeying the Michaelis-Menten law.
The advantage of this approach is that the modeler need know nothing of numerical analysis and can nonetheless treat complex, non linear-systems. Cheap versions for IBM-compatible personal computers are available.

Additional key words : *Network thermodynamics, compartmental systems, coupling of fluxes, chemical reactions.*

RÉSUMÉ

SPICE, un logiciel de simulation pour physiologistes.

Cet article présente un logiciel, appelé SPICE, pour simuler un certain nombre de problèmes de physiologie végétale. Bien qu'ayant été développé à l'origine pour simuler et mettre au point des circuits électriques et électroniques, il est depuis quelques années utilisé en physiologie humaine et animale.
Après avoir présenté les principales caractéristiques et possibilités de ce logiciel, 3 exemples simples illustrant son utilisation sont donnés : un modèle de transport d'eau à travers le végétal, un couplage eau-solutés à travers une membrane et une simulation d'un processus suivant la loi Michaelis-Menten
Des versions peu chères pour microordinateurs existent.

Mots clés additionnels : *Thermodynamique en réseaux, modèles à compartiments, couplage de flux, réaction enzymatique.*

I. INTRODUCTION

To varying degrees, experimental science requires the construction of models and the use of a simulation approach. In fields such as agronomy, bioclimatology, or physiology, many processes can be viewed as an exchange of matter and/or energy between different compartments of a complex system. Among several tools available to solve such problems, a circuit simulation package named SPICE has been increasingly used. Its original purpose was to help electrical engineers. Later it was recognized as a practical simulator for network thermodynamic models and has been used especially in animal and human physiology.

SPICE has three main features :

1) it is a very suitable tool for dealing with coupled fluxes of different kinds as they are formulated in the language of thermodynamics of irreversible processes ;

2) it emphasizes the connections between structures and functions, and allows one " to put together into a functioning whole a lot of pieces we may have observed as parts of a complicated system " (MIKULECKY, 1983) ;

3) it solves the system of equations corresponding to the behavior of the system.

For these reasons we believe that SPICE can be of great interest to many researchers. The purpose of this paper is to introduce this circuit simulation program

and to provide a few examples illustrating its use in the field of physiology.

A. What is SPICE ?

SPICE is a program for the simulation of electric and electronic circuits aimed at assisting in the development of such circuits. It was developed by the Laboratory of Electrical and Electronical Engineering at the University of California at Berkeley (USA). New versions, more flexible and more powerful, have been developed regularly since 1972. Several similar programs are available today, SPICE being the most widely distributed. It can be used on both mainframe and personal computers (*).

B. Use of SPICE for simulation of physiological problems

At first sight, it may seem strange to apply a program for electric circuits to simulations in physiology. However, a brief review of some historical and methodological facts will demonstrate the validity of this idea.

1. Use of electrical analogies

Such analogies have been used for a long time in animal and plant physiology (DAINTY, 1960 ; SANDERS et al., 1971). The same terms (e.g. resistance) are even applied to different but analogous phenomena expressed by formally similar laws.

2. Thermodynamics of irreversible processes (TIP)

In the 1950's, KEDEM & KATCHALSKY (1958, 1963a, b, c) were undoubtedly pioneers in the use of TIP for the phenomenological description of flow-force relationships in biological membranes. This theoretical approach has spread widely and has been applied in many fields of physics, chemistry and biology.

3. Network thermodynamics (NT)

In the same way that TIP can be considered a generalization of classical thermodynamics, NT can be viewed as an extension of TIP. This method of analysis developed along two lines, one based on line graphs (PEUSNER, 1970) and the other on " bond graphs " (OSTER et al., 1973).

NT has a double basis :

1) A generalization of the notions of fluxes J and forces X used in electricity, fluid mechanics, chemical thermodynamics and TIP (THIERY, 1983 ; CHAUVET, 1987). " Each process involving energy can be decomposed into a flow of material and the force responsible for this flow. The product JX takes the value of a power, an instantaneous energy, which may be stored, consumed or transported "(ATLAN, 1976). The generalized displacement and the generalized momentum (by analogy with the terms used in mechanics) are also used.

2) The use of network simulation programs.

NT is, so to speak, a powerful formal language that can be used for solving many problems of mass and energy transfer, particularly in biological and chemical systems. One proceeds as follows :

— Choose a topological representation of the biological system in the form of a network containing the various appropriate elements.

— For each element, the flows, the constitutive driving forces and the relationship between these two quantities are defined. An element can be a one-port if it is crossed by a single type of mass or energy, or an n-port in the case where there is more than one flow. For instance a resistor and a semi-permeable membrane allowing no active transport are one-ports. On the other hand, when representing the energy budget of a leaf exchanging energy by radiation, convection or conduction and water vapor with the environment, one will regard this leaf as an n-port. The same will apply to a study of coupled flows of water and ions across a membrane or to a set of associated chemical reactions. Translation into the system's NT language leads to a description of the system by means of the constitutive relations of the elements and those of electrical networks in particular (Kirchhoff's law, ...). It is thus possible to make an electrical description of how the system operates by using elements R, C, L and others.

Two alternatives are then available to understand how the system works :

— using direct numerical analysis to solve the set of equations describing the system ;

— using a circuit analysis program.

A circuit description generally involves characterizing the elements in the circuit and indicating their position in relation to the network nodes as well as the boundary conditions. Then the system of equations corresponding to the system's operation with initial conditions is automatically solved. This step therefore does not need be handled directly. Since many similar programs (SPICE is one of the most extensively used), both powerful and easy to use, are currently available, one can understand the major practical advantage of translating a problem in terms of NT. We purposely will not consider here the theoretical advantages of this formalization (MIKULECKY, 1983), since they are independent of the program used.

---

*Practical information

2G6, the latest SPICE program written in Fortran 5 (or 77) was developed at the University of California at Berkeley in 1983. Several versions are available depending on the type of computer and operating system (CDC, DEC, VAX (UNIX or VMS), IBM, etc...)

A new program in C language, named SPICE 3A. 7 was put on the market in March 1986. In spite of its efficiency, this program is of limited interest to physiologists for it does not allow the use of dependent polynomial sources, thus reducing its usefulness for physiological simulations.

These versions are available on magnetic tape for about $ 100.

SPICE programs are also available for IBM-compatible personal computers. For example INTUSOFT (P.O. Box 6607, San Pedro CA 90734, USA) sells versions of SPICE derived from 2G6 which are more efficient in both ouput and simulation types than the most recent versions for computers developed at the University of California at Berkeley. These versions for PCs sell for about $ 200-250.

Comment

The electrical analogue is not the only possibility, nor always the best. For various reasons, it is the one most commonly used today. However programs for hydraulic engineering analysis could be as appropriate in certain cases. Obviously, it would be better to use a fully network thermodynamics-oriented program rather than translating into the language of specialized simulation programs. It is hoped that such a program will be developed in the near future.

Now that we have presented the principles underlying the use of SPICE in physiology, we will give a brief description of this simulation program.

II. BRIEF DESCRIPTION OF SPICE

Using SPICE (i.e. writing a program in SPICE language) involves describing each element of the circuit in order to represent the system to be investigated and the conditions it will be submitted to.

A. Elements (table 1)

TABLE 1

SPICE Circuit Elements.

Eléments de circuit de SPICE.

Linear elements
— Resistor (R)
— Capacitor (C)
— Inductor (L)
— Mutual Inductors (K)
— Independent Voltage Source (V)
— Independent Current Source (I)
— Linear Dependent Source (E, F, G, H)

Non-linear Elements
— Non-linear Dependent Sources (E, F, G, H)
— Diode (D)
— Bipolar Junction Transistor (Q)
— Junction Field-Effect Transistor (J)
— Insulated-Gate Field-Effect Transistor (M)
— Transmission line

The type of each element is defined by the first letter (e.g.: (R)esistor, (C)apacitor, ...). The name (e.g.: CAP 2) can be any combination of 7 alphanumeric characters. It is followed by two node numbers identifying its branch and then by the value(s) of the parameter(s) defining the electrical characteristics of this element.

ex : VCAP2   8   0   12

This line sets a constant voltage source of 12 volts between the connection element nodes 8 and node 0. Node 0 is ground. The circuits studied later will show other examples.

The main elements of SPICE can be classified somewhat arbitrarily into 3 categories :

a) Linear elements include resistors, capacitors, inductors, independent voltage and current sources. The latter can be constant, or time-dependent. There are five independent source functions : exponential, sinusoidal, piece-wise linear, pulse and single frequency. It is also possible to compose variable resistors and capacitors.

* Voltage sources, in addition to being used for circuit excitation, are the " ammeters " for SPICE, that is voltage sources of value zero may be inserted into the circuit for the purpose of reporting current in a given branch.

b) Non linear elements essentially include semiconductor devices. As the latter have not been used for physiological simulation yet, we will not consider them here.

c) Dependent or controlled sources are extremely useful elements conferring considerable simulation power to SPICE. They produce a voltage or a current that may depend on one or several voltages of currents existing elsewhere in the circuit. Four types of controlled sources are available :

— current-controlled voltage sources (H),
— voltage-controlled voltage sources (E),
— voltage-controlled current sources (G),
— current-controlled current sources (F).

There are 2 major restrictions affecting these functions :

— the functions must be expressed as polynomials in which the exponents of variables must be positive integers ;
— a dependent source can depend on one or several voltages (up to 6), or one or several currents. It cannot depend simultaneously on a voltage and a source. This condition, however, can be easily circumvented.

Moreover, the availability of the source code for academic research allows incorporation of special functions (e.g. hyperbola for Michaelis-Menten equation, Goldman's equation for membrane transport).

Usually, the definition of a non-linear dependent source takes the form :

$$
\left.
\begin{array}{l}
F \\
G \\
H \\
\\
J
\end{array}
\right\}
\quad
\begin{array}{l}
\text{Name } N^+ \ N \ \text{POLY(n) } NC1^+ \ NC1 \ NC2^+ \\
NC2 \ a_0 \ a_1 \ a_2 \ a_3
\end{array}
$$

The current (F or G) or the voltage (H or E) between nodes N^+ and N is a polynomial of n variables (currents or voltages) situated between nodes $NC1^+$ and $NC1^-$, the polynomial coefficients being successively a_0, a_1, a_2, a_3, ...

B. Control statements

The control statements serve to specify the desired analysis and output :

New versions of SPICE do not need explicit control lines for the output : they store all the output and permit one to trace any combination of these. In the same way,

some CAE programs allow one to generate the statements directly from the design of the circuit on a graphic screen using a mouse.

C. Simulation

SPICE allows 3 majors types of simulation to be performed :

— A direct current analysis (DC Analysis) which corresponds to a steady state analysis.

— A transient analysis giving the time-dependent response of the system over an interval to be specified.

— An alternating current analysis (AC analysis).

Several alternatives are available among these 3 categories (table 2). For example for large-signal sinusoidal

TABLE 2

SPICE Analysis Capabilities.

Différents types d'analyses faites par SPICE.

DC Analysis
- — DC Operating Point
- — Linearized Device Model Parameterization
- — Small-Signal Transfer Function
- — Small-Signal Sensitivities
- — DC Transfer Curves

Transient Analysis
- — Time-Domain Response
- — Fourier Analysis

AC Analysis
- — Small-Signal Frequency-Domain Response
- — Noise Analysis
- — Distorsion Analysis

simulations, a Fourier analysis of the output waveform can be performed. The DC component and the first 9 components are determined. Likewise, different signal analyses can be obtained. To date, however, the sample DC and transient analyses have been most commonly used for physiological simulations.

III. EXAMPLES OF SIMULATION OF PHYSIOLOGICAL PROBLEMS

Three simple examples will be presented to demonstrate how the most common elements of SPICE can be applied in 3 fields of physiology. Detailed explanations are provided to initiate physiologists into the use of this program.

A. Whole plant flow model (fig. 1)

Water enters vascular plants in liquid form through the root system. It moves in this form along very fine capillaries (xylem vessels) through the whole plant. Upon reaching the leaves, it passes from the liquid to the vapor phase and is released through the stomata
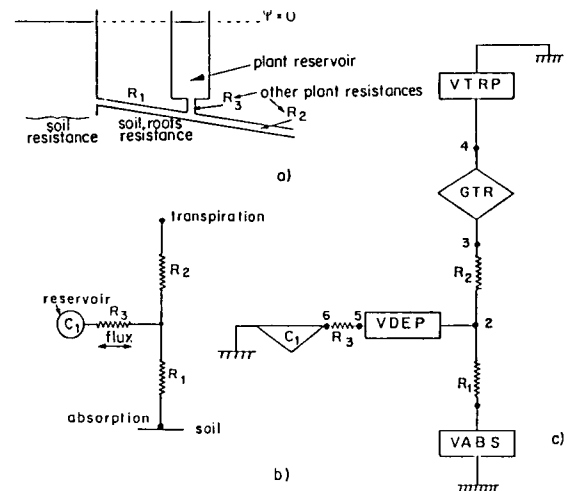

Figure 1

Whole plant flow model.
a) *hydraulic analogy*,
b) *representation of the same system using equivalent electrical elements*,
c) *the corresponding SPICE flow model (see § 3.1)*,
d) *graph of the flows.*

Modèle de transport d'eau à travers un végétal.
a) *analogie hydraulique*,
b) *représentation du même système en analogie électrique*,
c) *le circuit SPICE correspondant (voir § 3.1)*,
d) *graphe des flux.*

into the atmosphere. The main driving force for this water flow is transpiration, which maintains a gradient of water potential from the ground to the leaves analogous to voltage. If the amount of water absorbed by the roots is equal to that evaporated from the leaves, the flux is conservative and can be represented by Ohm's law type relations. If these amounts are unequal (wilting, rehydration), the flux is non-conservative. In addition to resistors, the evolution of the water balance and its dynamics can then be described in terms of water capacitance analogous to electrical capacitance. In the

present example, which only considers the flow in liquid form, the plant is schematically represented by the flow model in figure 1 including a soil (constant level reservoir) supplying water to the plant. The latter is made up of 3 resistors and one constant capacitance reservoir (simplified view).

Simulating involves following fluxes and voltages as a function of time in response to imposed transpiration. This transpiration increases instantaneously, levels off for a while, and decreases linearly and rather slowly.

Therefore, the input consists of the parameter values and the initial conditions (voltage at boundaries, transpiration). The output consists of the instantaneous or cumulative currents along with the voltage at the different nodes.

The corresponding listing is as follows :

```
** MODEL : P1A DATE
** TIME CONSTANT
** PARAMETERS :   3   resistors   R1   =   90
bar · mg⁻¹ · cm² · s
** R2 = 60
** R3 = 150
** PARAMETERS :   1   constant capacitance   =
2.5 mg · cm⁻² · bar⁻¹
```

* DESCRIPTION OF THE CIRCUIT

```
R1   1   2    90.0
R2   2   3    60.0
R3   5   6   150.0
C1   0   6     2.5   IC = 0
```

* MEASUREMENT OF THE FLUXES

```
VABS   0   1   0.0
VDEP   5   2   0.0
VTRP   4   0   0.0
```

* IMPOSED TRANSPIRATION

```
GTR   3   4    7   1.0
VCLOCK        7   0   PWL (0   0.0   300   0.0
+             301   0.006   3300   0.006   5400   0.0)
RCLOCK        7   0   1.0
```

* MEASUREMENT OF THE CUMULATIVE FLUXES : CABS, CDEP, CTRP

```
CCABS   100   0   1.0
FCABS   100   0   VABS   – 1.0
RCABS   100   0   1E7
CCDEP   110   0   1.0
FCDEP   110   0   VDEP   – 1.0
RCDEP   110   0   1E7
CCTRP   120   0   1.0
FCTRP   120   0   VTRP   – 1.0
RCTRP   120   0   1E7
```

* SIMULATION

```
.TRAN   30   6000   UIC
.PLOT   TRAN   I(VABS)   I(VDEP)   I(VTRP)
.PLOT   TRAN   V(100)   V(110)   V(120)
.END
```

Comments

— The capacitance of the capacitor is 2.5 farads for SPICE, but 2.5 mg · bar⁻¹ · cm⁻² for the physiologist. IC = 0 means that its initial voltage is 0 volt. Therefore the water potentials (expressed in bars) of both the soil and the plant are equal at the start.

— Three ammeters (sources of zero voltage) are used to measure the currents in the branches : VABS, VDEP, VTRP.

— To impose the desired transpiration, i.e. the current flowing from node 3 to node 4, 2 elements are used :

a) a source G (voltage-dependent current source) ;

b) a special voltage source (VCLOCK) between nodes 0 and 7 of an independent auxiliary circuit whose value varies linearly with time (PWL = piece-wise linear). Here, the transpiration rises from 0 to 0.006 volts (0.006 mg · cm⁻² · s⁻¹ for the physiologist) within 1 second (between the 300th and the 301st second), remains at this level until time t = 3 300 s, and returns slowly to 0 within 2 100 s. As indicated by the source G, the current flowing between nodes 3 and 4 will be equal, at any time, to one times the voltage between nodes 7 and 0.

```
GTR   3   4        7   0          1.0
      controlled   controlling   coefficient
      nodes        nodes
```

The cumulated fluxes are read by means of 3 small independent auxiliary circuits in which a capacitor is charged with current equal to one of the fluxes of the main circuit.

In each auxiliary circuit, one requires, through a source F, that the current be equal to a current measured in the main circuit (e.g. between nodes 100 and 0, it is the current measured by the ammeter VABS that will flow). The integral of the current over the time interval is equal to the charge accumulated within the capacitor : at any given time, the potential drop across the capacitor (ex : V(100)) is equal to V = Q/C = Q since C = 1. From a node's voltage, one can thus obtain at each time the cumulated amount of water having left a reservoir (or having entered this reservoir) over a given time interval.

In the output, the following is required :

— a transient analysis (.TRAN) of the system's evolution from time t = 0 to time t = 6 000 s, with one point printed every 30 s from time t = 0 ;

— a graph showing the evolution of currents and voltages at different points of the main circuit and of the auxiliary circuits.

MOLTZ *et al.* (1979) have given another example of the use of SPICE — without the listing of the program — for studying quantitative water relations in plant tissues.

B. Coupled flow of water and solute across a membrane (fig. 2)

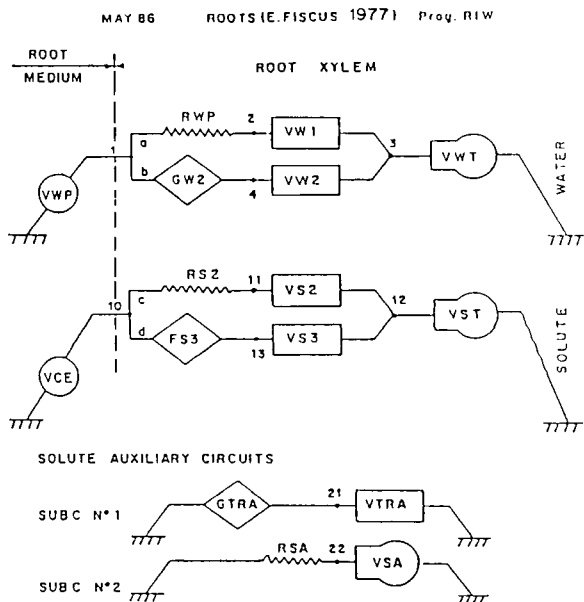This example will show how equations can be translated into SPICE language and how the coupling of

Figure 2a

Simulation of coupled flow (water and ions) using a SPICE program. This is the root model proposed by FISCUS (1977)

Simulation de flux couplés d'eau et d'un soluté : le circuit SPICE. Cet exemple est le modèle de racine proposé par FISCUS (1977).

Figure 2b

Listing of the program of example illustrated figure 2a.

Programme correspondant à l'exemple illustré figure 2a.

different kinds of fluxes is expressed. This will provide better insight into :

a) the use of n-ports, i.e. of elements having several kinds of in- and outflows ;

b) the " physical " separation of the various kinds of flows : only one kind of flux flows through a single branch. The theoretical coupling expressed in the equations essentially occurs through the dependent sources (F, G, H, E) that allow the voltage and/or the potential at one point to be linked with the potential and/or the voltage at another point.

Therefore, instead of relying on a schematic diagram supposedly representing the global behavior of a system (previous example), we will start from two equations describing the coupled flows of water and solutes across a membrane in a simple case (fig. 3).

$$J_v = Lp(\Delta P - \pi_i) - Lp\,\sigma_s\,\Delta\pi_s \qquad (1)$$

$$J_s = C_0(1 - \sigma_s)J_v + RT\,\Delta Cs + J_s^* \qquad (2)$$

$$= C_0(1 - \sigma_s)J_v + \omega\,\Delta\pi_s + J_s^* \qquad (2')$$

terms :   solvent drag   diffusive   active transport
branches =   d   c   d

with :

J_v = total volume flux.

ΔP = $P_1 - P_2$ = difference of hydrostatic pressure across the membrane.

$\Delta\pi_i$ = π_{1i} π_{2i}, osmotic pressure difference due to non-permeable solutes (for which $\sigma = 1$).

$\Delta\pi_s$ = π_{1s} π_{2s}, osmotic pressure difference due to permeable solutes (for which $\sigma < 1$).

Lp = coefficient of filtration or hydraulic conductivity.

C_0 = (C1 + C2)/2, C1 and C2 being the concentration of either side of the membrane respectively. In certain situations (THOMAS & MIKULECKY, 1978), it can also be, as in the present example, the concentration of the outside compartment.

σ_s = reflection coefficient for permeable ions.

ω = coefficient of solute mobility.

R = universal gas constant.

T = temperature (Kelvin).

J_s^* = active solute flux.

Thus we have 2 kinds of flux (considering only one solute) each of which can be considered as the algebraic sum of 2 or 3 elementary fluxes, each corresponding to a term of the right-hand side of equations 1 and 2. Our aim is to represent these terms by appropriate dependent sources or other elements.

1. *Representation of flux J_v*

This form of the flux equation is commonly used in TIP and often the most convenient for SPICE. J_v will therefore be considered as the sum of 2 terms XiFi. Xi is a coefficient, Fi a force, each of these 2 components of J_v will flow through a branch (fig. 2a).
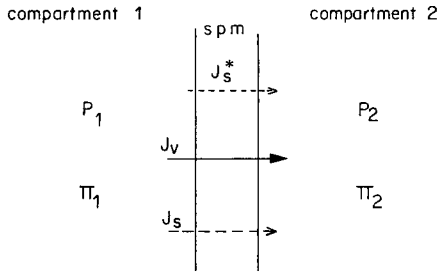
Figure 3

System of two compartments separated by a semipermeable membrane (spm) containing an active solute uptake mechanism capable of moving solutes against a potential gradient ; J_s = total solute flow ; J^*_s = active solute flow ; J_v = total volume flow ; P_1, P_2 : hydrostatic pressure of compartments 1 and 2 respectively ; π_1, π_2 : osmotic pressure of compartments 1 and 2 respectively.

Système à 2 compartiments séparés par une membrane semi-perméable (spm) siège d'une absorption active de soluté ; J_s = flux total de soluté ; J^*_s = flux actif de soluté ; J_v = flux volumique total ; P_1, P_2, pression hydrostatique des compartiments 1 et 2 respectivement ; π_1, π_2 pression osmotique des compartiments 1 et 2 respectivement ; les flèches correspondent au sens positif.

Branch a consists of :

$$J_v = Lp(\Delta P - \Delta \Pi_i) - Lp\ \sigma_s\ \Delta \pi_s$$

$$X_1 \quad \text{Force 1} \qquad X_2\ \text{Force 2}$$

— a resistor RWP taking the value l/Lp. The current flowing across this branch will have the value Lp P*, with P* = $\Delta P - \Delta \pi_i$ if the voltage across this branch equals ΔP^* (see below) ;

— an ammeter VW1 measuring the current in this branch.

ΔP^* is fixed by a voltage source VWP = ΔP^* between nodes 0 and 1. This grounded source puts node 1 at a potential $\Delta P^* = 1$ volt (1 bar for the physiologist), resulting in a potential of 1 bar between nodes 1 and 2 since nodes 2 and 3 are grounded. The element VWT will be considered below.

Branch b consists of a single active element (in addition to an ammeter VW2 used to measure the voltage) : element GW2 which is a current source controlled by a voltage equal to $\sigma_s\ \Delta\pi_s$:

GW2 1 4   POLY (1)   10   12   0.0   -2.3E - 06

    controlled nodes   controlling nodes   Lp

The current flowing through branch b will be equal to $-$ Lp $\sigma_s\ \Delta\pi_s$.

The VWT element (like VSA, see below) is composite, because it acts both as an ammeter and a non-null voltage source. Flux J_v, the current passing through VWT, is the sum of the 2 fluxes passing through branches a and b respectively :

$$J_v = Lp\ \Delta P^* - Lp\ \sigma_s\ \Delta\pi_s\ .$$

This first sub-circuit corresponds to equation 1.

2. *Representation of solute flux J_s*

We follow the same procedure as above. Flux J_s is made up of 3 elementary fluxes (solvent drag or convective term, diffusive, active transport) which must be written in the form of a product XiFi. As shown by equation 2′ only the solvent drag term does not meet this requirement, because it is the product of 2 different variables : a voltage (C_1) and a flux (J_v). As SPICE does not accept this kind of source, one must first use a small auxiliary circuit to fix a node voltage " $V(J_v)$ " equal to the current J_v. Then a voltage-dependent current source multiplies $V(J_v)$ by C_1 to give the solvent drag contribution. Then, to avoid multiplying the branches, the solvent drag and active transport terms are grouped on one side (branch d) while the diffusive term is put on the other side (branche c).

Conversion of the convective term $C_1 (1 - \sigma_s) J_v$. To convert C_1 into a current, we create a voltage-dependent current source, a source G named GTRA, such that :

$$GTRA = C_1(1 - \sigma_s) = \pi_1(1 - \sigma_s)/RT =$$
$$= \pi_1(1 - 0.87)/24.37\ 10^3 = 5.33\ 10^{-6}\ \pi_s.$$

This is a polynomial function of σ_s reduced to a single term, which will be accomplished by use of an auxiliary circuit (see auxiliary circuit n° 1, fig. 2a). This circuit includes 2 nodes, 0 and 21, between which a current (GTRA) flows. This current is equal to 5.33 E - 0.6 π_1, where π_1 is a voltage source (VCE) located between nodes 1 and 10 in the main circuit, representing the osmotic pressure of the outside compartment. The element line designating this source will be written :

GTRA   0   21   POLY(1)   10   0   0.0   5.33 E - 0.6 .

The convective term of equation 3.2 thus becomes a current that depends on 2 currents, J_v (measured by the ammeter VTRA), rather than on a voltage and a current.

The creation of branch d, which includes both the convective and the active terms, requires the use of a sub-circuit corresponding to flux J^*_s. This will include :

— a voltage source VSA taking the value J^*_s (in this case, J^*_s = 7.5 E - 12 mole $\cdot$ cm^{-2} $\cdot$ s^{-1})   between nodes 0 and 22 (numbers are randomly assigned, except for the ground which must be zero). Then this source can also act as an ammeter ;

— a resistor RSA equal to 1. The current flowing through this circuit will be :

$$V/R = J^*_s\ .$$

In branch d, the flowing current will be the algebraic sum of the convective term (function of J_v and of GTRA) and the active transport term (equal to VSA). This current is therefore a polynomial function (with only 2 terms) of 3 variables being currents. It is a source F, named FS3, such that :

$$FS3 = GTRA \cdot J_v + J^*_s\ .$$

The expression of such a 3-dimensional polynomial (x_i, x_2, x_3 being the variables) as understood by SPICE is written:

$$F(x_1, x_2, x_3) = a_0 + a_1 x_1 + a_2 x_2 + a_3 x_3 +$$
$$+ a_4(x_1)^2 + a_5 x_1 x_2 + a_6 x_1 x_3$$
$$+ a_7(x_2)^2 + a_8 x_2 x_3 + a_9(x_3)^2 + a_{10}(x_1)^3 + \cdots$$

with GTRA = $x_1 : J_v = x_2$ and $J^*_s = x_3$, FS3 becomes:

FS3 $= a_3 x_3 + a_5 x_1 x_2$ with $a_5 = a_3 = 1$ all other coefficients being zero.

The element line corresponding to FS3 is written:

FS3   10   13   POLY (3)   VRTA   VWT   VSA   0.0   0.1   0.1

  controlled nodes   controlling nodes   coefficients

An ammeter (VS3) is also used to measure current FS3.

Branch c, which corresponds to the diffusive term, is simpler. The 2 voltage sources corresponding to the outside (VCE) and inside (VST) concentrations are located at nodes 10 and 12 respectively, in parallel with branch d. In the present example, VCE = 2 bars and VST = 0.2. The other element between nodes 10 and 11 is a resistor (RS2) with a value $1/\omega$ = 1.0E12 ohm (or mol · cm^{-2} · s^{-1} · bar^{-1}). There also is an ammeter VS2.

Note that ammeters are not always necessary. Their presence, however, allows the measurement of elementary fluxes that may be desired in the program output. They are also of great assistance in verifying calculations.

The simulation requested here is a steady state analysis (control card starting with DC with different values of the inside concentration (up to 2 bars by increments of 0.2 bar). In addition, the use of another control card (.ALTER) allows variations in one or several other parameters to be produced in the same simulation. E.g. in the present case, the outside hydrostatic pressure respectively takes the value 3 bars and then the value 10 bars. For each of these values the source VST varies from 0 to 2 bars by increments of 0.2 bar.

The program's listing corresponding to this membrane is in figure 2b.

THOMAS & MIKULECKY (1978), MINTZ et al. (1986) and THOMAS (1988) give other examples of different kinds of transport mechanisms involving coupled fluxes using SPICE.

C. Process obeying the Michaelis-Menten law (after WHITE & MIKULECKY, 1982)

Enzymatic processes (conversion of substrate to product catalyzed by an enzyme) or physiological processes (uptake of a substance by excised organ), frequently obey the Michaelis-Menten law:

$$v = Vmax \, S/(Km + S) \qquad (3)$$

v = velocity of the reaction or rate of uptake,
S = concentration of substrate or substance in the outside solution,
Vmax = maximum velocity of transport or rate of uptake km = Michaelis constant.

The preceding relation indicates that the velocity of formation of the product or substance (e.g. an ion) is a hyperbolic function of the substrate or ion concentration in the medium. Translated into SPICE language, the preceding relation is the expression of a voltage-dependent current. Unfortunately, the current versions of SPICE do not deal directly with quotients. Thus for any expression including a ratio, one must write using an auxiliary circuit that is not connected to the main circuit representing the biological system to be investigated. Let us assume here that a substrate S is converted to a product P. Two capacitors are placed, one at each end of the circuit. In the present case, their capacitance represents a volume following the equation:

$$C = \frac{\text{amout of substance (moles)}}{\text{concentration of substance (moles/liter)}} = \text{volume (liter)}$$

Initially, compartment S has a certain volume C and compartment P is empty. The rate of change of concentration of material produced, as measured by the ammeter VSP, will correspond to a concentration, since it is given by:

Rate of change of concentration in compartment = $\dfrac{\text{amount of substance added to or substracted from the compartment}}{\text{volume}}$.

Capacitors are used when the volume of compartments is limited or when this restriction is involved in the system's regulation. To represent a nearly infinite reservoir, the easiest would be to replace the capacitor by an independent voltage source.

The flow of material (or the reaction velocity) is given by equation 3. It is a function of the substrate concentration, i.e. of the voltage at note 1, and must therefore be represented by a voltage-dependent current source, hence by a G element. This controlling voltage will be

that at node 10 of the auxiliary circuit (fig. 4b), thus giving:

GMM   2   3   10   11   1

  controlled nodes controlling nodes proportionality
                                    coefficient

The current produced by GMM is linearly dependent on the voltage between nodes 10 and 11 (or 10 and 0) with a proportionality constant of 1.
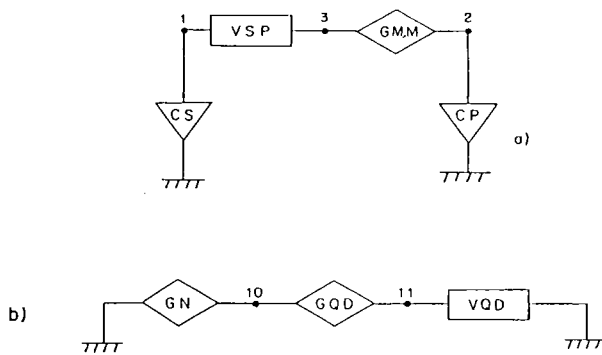
Auxiliary circuit (fig. 4b).

Figure 4

Schematic representation of a process according to the Michaelis-Menten equation using SPICE.
a) *main circuit,*
b) *auxiliary circuit.*
Further explanations are given in the text.

Circuit SPICE d'un processus suivant la loi Michaelis-Menten.
a) *circuit principal,*
b) *circuit auxiliaire.*
Pour plus d'information voir le texte.

The purpose of this circuit is to calculate the quotient v of equation 3. To this effect, the equation must take the form :

$$S \cdot Vmax = v\, Km + vS. \qquad (4)$$

Each term of this equation will be a source G. GN will represent the left term (numerator of 3) and GQD the right term (product of quotient and denominator of 3). If both sources are placed in series, the current generated by GN from ground to node 10 must equal the current across GQD since there is no accumulation element. The voltage at node 10 will vary as a function of the current flowing through. According to equation 4, the source GN is a linear function of the concentration S, and will be written :

GN   0   10   1   0   Vmax

    controlled nodes   controlling nodes coefficient

The current flowing from node 0 to node 10 is Vmax-fold the voltage between nodes 1 and 10 (e.g. substrate concentration). The GQD source is a function of 2 variables : v = velocity of formation of the product (voltage between nodes 10 and 11) and S = substrate concentration (voltage at node 1). The GQD source will therefore be a polynomial function written as follows :

current GQD $= 0 + Km\, v + 0S + 0(v)^2 + 1\, vS$.

Hence the coefficients are 0, Km, 0, 0, 1. As a result, the SPICE description of this source is written :

GQD   10 11 Poly (2)   10 0 1 0   0 Km 0 0 1

           controlled   controlling   polynomial
            nodes   nodes   coefficients

The order in which the controlling nodes are chosen determines the order of the coefficients. Another form equivalent to GQD may be :

GQD   10 11   POLY(2)   1 0 10 0   0 0 km 0 1

Hence the simulation program for this chemical reaction, in which the dynamics of substrate formation (or substance uptake by the excised organ) are investigated as a function of time and value S, Km and Vmax, will be written :

** PROGRAM : simulation of transport according to the Michaelis-Menten equation

* MAIN CIRCUIT
CS   0   1   value of capacitance   IC : initial voltage
VSP   1   2   0.0
GMM   2   3   10   11   1.0
CP   2   0   value of capacitance   IC : initial voltage

* AUXILIARY CIRCUIT
GN   0   10   1   0   Vmax
GQD   10   11   POLY(2)   1   0   10   0   0.0   Km
0.0   0.0   1.0
VQD   11   0   0.0

* SIMULATION
.TRAN   TSTEP   TSTOP   UIC
.PLOT   TRAN   V(1)   V(2)   V(3)   V(10)
.PLOT   TRAN   I(VSP)   I(VQD)
.END

It is also possible to obtain the same results by directly incorporating the source coding for a Michaelis-Menten type relationship. Beside, the evolution with time of the different substances from the following enzymatic reaction can also be simulated :

$$E + S \leftrightarrow E\dot{S} \leftrightarrow E + P.$$

with E = Enzyme ; S = Substrate ; P = Product ;
     ES = Enzyme — substrate complex.

Other more sophisticated examples for simulating cellular pharmacokinetics (WHITE & MIKULECKY, 1982 ; THAKKER *et al.*, 1982) or reaction diffusion systems (WYATT *et al.*, 1980 ; MAY & MIKULECKY, 1982) can be found, illustrating the capabilities of SPICE in this domain.

IV. STRENGTHS AND WEAKNESSES OF SPICE

A. Strengths

1) Equations, particularly sets of differential equations, are easier to formulate than to solve. Many physiologists can write and understand certain kinds of equations, but often lack the specific knowledge of mathematics especially in numerical analysis required to solve them. As mentioned previously, SPICE is very convenient to use in this respect, because it usually relieves physiologists from such tedious work. It may be assumed that a physiologist would rather spend his time trying to better understand his system than learning techniques of solving differential equations.

Remark : The integration method used by SPICE is the trapezoidal method. As an alternative, gear's

method is available. Concerning this point the reader may refer to Nagel (1975).

2) On the other hand, the process of expressing a physiological or biochemical problem in the language of SPICE compels one to explore the various aspects of this problem, and place emphasis upon the structure representing this system. This is an essential point, for elementary equations are frequently mistaken for structure. For instance, most global models of water and mineral uptake by the roots are based on equations 1 and 2. Some authors, however, believe that " one should use a 3-compartment model rather than these equations ". This is not the relevant point. The quantitative approach to the functioning of a system is obtained by applying basic equations to a particular structure. So the purpose is to define the structure and basic equations rather than to replace a structure by a law. Hence the above equations which are valid at the membrane level produce different effects depending on whether the structure consists of one or several compartments.

B. Weaknesses

SPICE has a number of limitations which can be disappointing or even deterrent. Yet these weaknesses tend to be remedied in the new versions and should be considered as temporary.

1. Input

It was shown that the input cannot deal directly with quotients or polynomials with negative exponents. Likewise, exponential, logarithmic and hyperbolic functions cannot be written directly. They require the construction of an auxiliary circuit, for the standard versions of SPICE. Other circuit simulation programs (ASTEC for instance) permit a more direct description of non-linear relations. That is, one enters the equations for the constitutive relations directly in a FORTRAN-like expression.

2. Simulations

Many additional types of analysis can be made on electrical networks and would also prove useful in

physiological simulation (e.g. : parameter optimization, statistical analysis for evaluating circuit properties for a certain range of parameter values, etc...). It is only because these analyses were already available in the program library at the University of Berkeley that the authors of SPICE did not try to insert them into their program ! So if " network thermodynamics is completely independent of electronics and electrical network theory " (MIKULECKY, 1983), SPICE is still very dependent on electrical circuits, due to its origin.

V. CONCLUSION

We have presented some very simple examples of the use of SPICE for simulating problems of transfer of matter and energy in biological systems. The simplicity of these examples does not fully exploit the real advantages of SPICE, which are only realised in much more complex problems. Unlike techniques using higher mathematics requiring an explicit formulation in terms of equations, SPICE rests on schematic depictions of the system. The present use of SPICE in such different fields as classical physiology, membrane biophysics, pharmacokinetics, electrochemistry of vision provide a good illustration of its usefulness for biologists. The advantage of this approach to simulation is that the modeler need know nothing of numerical analysis and can nonetheless treat complex, non-linear systems. In this regard SPICE is not necessarily the easiest simulation program to use (ASTEC is more user-friendly) but it is very powerful, is universally available, has been adapted for nearly all kinds of machines, and is very cheap or free.

REFERENCES

Atlan H., 1976. Les modèles dynamiques en réseaux et les sources d'information en biologie. In : « *Structures et dynamiques des systèmes* ». Maloine, Paris, 95-131.

Chauvet G., 1987. *Traité de physiologie théorique*. Vol. 1, Masson, 76-83.

Dainty J., 1960. Electrical analogues in Biology. In : "*Models and analogues in Biology* ". Symposia of the Society for Experimental biology, nx XIV, Cambridge Univ. press., 140-151.

Fiscus E. L., 1977. Determination of hydraulic and osmotic properties of soybean root systems. *Plant Physiol.*, 59, 1013-1020.

Kedem O., Katchalsky A., 1958. Thermodynamic analysis of permeability of biological membranes to non electrolytes. *Biochem. Biophy. Acta*, vol. 27, 229-246.

Kedem O., Katchalsky A., 1963a. Permeability of composite membranes. Part 1. Electric current, volume flow and flow solute through membranes. *Trans. Faraday Soc.*, 59, 1918-1930.

Kedem O., Katchalsky A., 1963b. Permeability of composite membranes. Part 2. Parallel elements. *Trans. Faraday Soc.*, 59, 1931-1940.

Kedem O., Katchalsky A., 1963c. Permeability of composite membranes. Part 3. Series array of elements. *Trans. Faraday Soc.*, 59, 1941-1953.

May J. M., Mikulecky D. C., 1982. The sample model of adipocyte hexose transport kinetic features, effect of insulin and network thermodynamic computer simulations. *J. Biol. Chem.*, 257, 11601-11608.

Mikulecky D. C., 1983. Network thermodynamics : a candidat for a common language for theoretical and experimental biology. *Am. J. Physiol.*, 245 (Regulatory Integrative Comp. Physiol. 14) : R1-R9.

Mintz E., Thomas S. R., Mikulecky D. C., 1986. Exploration of apical sodium transport mechanisms in a epithelial model by network thermodynamic simulation of the effect of mucosal sodium depletion :

1. Comparison of three different apical sodium permeability expressions. *J. Theor. Biol.*, 123, 1-19. II. An apical sodium channel and amidonite blocking. *J. Theor. Biol.*, 123, 21-34.

Moltz F. J., Kerns D. V. Jr, Peterson C. M., Dane I. M., 1979. A circuit analog model for studying quantitative water relations of plant tissues. *Plant Physiol.*, 64, 712-716.

Nagel L., 1975. *SPICE 2. A computer program to simulate semiconductor circuits.* Memorandum ERL-M 520. Electronics research laboratory, College of Engineering, University of California, Berkeley.

Oster G. F., Perelson A., Katchalsky A., 1973. Network thermodynamics. *Q. Rev. Biol.*, 6 (1), 1-134.

Peusner L., 1970. *" The principles of Network Thermodynamics and biophysical applications. "* Ph. D. Thesis, Harvard Univ. Cambridge MA (USA).

Sanders F. E., Tinker P. B., Nye P. H., 1971. Uptake of solutes by multiple root systems from soil. 1. An electrical analog of diffusion to root systems. *Plant soil.*, 34, 453-466.

Thakker K. M., Wood J. M., Mikulecky D. C., 1982. Dynamic simulation of pharmacokinetic systems using the electrical circuit analysis program SPICE 2. *Comp. Prog. Biomed.*, 15, 61-72.

Thiery J. M., 1983. Systèmes thermodynamiques. Applications en biologie de la thermodynamique en réseaux. A.M.T.B. *Ecole d'Automne de Biologie Théorique,* 3ᵉ session, 19 septembre-7 octobre, Abbaye de Solignac (Haute-Vienne).

Thomas S. R., Mikulecky D. C., 1978. A network thermodynamic model of salt and water flow across the kidney proximal tube. *Am. J. Physiol.*, 235 (Renal fluid electrolyte physiol 1) : F630-F648.

Thomas S. R., 1988. Modèle longitudinal du tube proximal du rein par la thermodynamique en réseaux. *IIᵉ Séminaire de l'Ecole de Biologie Théorique de Solignac,* 1-3 septembre 1987. A paraître fin 1988.

White J. C., Mikulecky D. C., 1982. Application of network thermodynamics to the computer modeling of the pharmacology of anticancer agents : a network model for methotrexate action as a comprehensive example. *Pharmacol. Ther.*, 15, 251-291.

Wyatt J. L. Jr, Mikulecky D. C., Desimone J. A., 1980. Network modeling of reaction-diffusion systems and their numerical solution using SPICE 2. *Chem. Eng. Sci.*, 35, 2115-2128.