*Appl. Math. and Comp. Sci., 1994, vol.4, No.2, 193–202*

# DISTRIBUTED MODELLING OF CELL POPULATION

WOJCIECH JĘDRUCH*, JACEK WANIEWSKI**

A distributed approach to modelling of population processes is discussed, and a few examples of simulations generated by an abstract universe — a universal modelling environment — are presented.

## 1. Distributed Modelling

The growing power of computers makes possible an approach to the modelling of physical systems called distributed modelling. In this case local rules of interaction between elements of a system are specified, and then an evolution of the system consisting of many such elements is investigated by computer simulation. Using this approach, a complex global behaviour of a model is obtained as a result of many simultaneous, distributed in space, local and simple interactions. Using distributed modelling, for example, instead of creating and solving numerically equations governing the behaviour of a turbulent flow in a fluid, one can model the flow by simulating directly the motions of the fluid constituent particles.

Langton (1989) strongly recommends the distributed approach for modelling biological processes. He states that it is easier to generate complex behaviour from the application of simple, local rules than to generate it from the application of complex, global rules. This is because complex global behaviour is usually due to non-linear interactions occurring at the local level. With bottom-up specifications, the system computes the local, non-linear interactions explicitly and the global behaviour — which was implicit in the local rules — emerges spontaneously, without being treated explicitly. With top-down specifications, however, local behaviour must be implicit in global rules.

Toffoli (1984) discusses the distributed modelling by means of cellular automata as an alternative to differential equations. He claims that as long as all computations had to be done by hand, it paid to stylize the physics in a certain direction so as to be able to handle the resulting mathematics. But few differential equations have a closed-form solution and if the equations have to be solved numerically, it appears that there are at least three levels removed from the physical world they try to represent. That is, first we stylize physics into differential equations, second we force the equations into discrete time and space, third we truncate the real-valued variables into finite computer words. In such cases the use of cellular automata instead of differential equations is a tempting alternative.

* Faculty of Electronics, Technical University of Gdańsk, ul. Narutowicza 11/12, 80–952 Gdańsk, Poland

** Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, ul. Trojdena 4, 02–109 Warszawa, Poland

Distributed models are natural for many physical, chemical or biological systems, whose behaviour is a result of interactions of many active elements distributed in space. They could be especially beneficial when new, unforeseen properties of the modelled system are likely to emerge while it evolves in time or when beside a mere numerical agreement with a physical system the model should map its structure and topology. For such systems, distributed modelling can be an attractive substitute for models based on differential equations apparatus. Moreover, the distributed model can be used as a first, prototype model of a system, becoming a base for later constructing a formal mathematical model.

There seems to be at least three possible ways of using the distributed modelling in the field of the cell population dynamics, namely:

1. Modelling of the population dynamics in the manner similar to the modelling of the chemical reaction kinetics — by simulating the movement of cell individuals and their encounters and interactions with other cells individuals or drug particles.
2. Modelling of development of various structures consisting of cell individuals.
3. Modelling of development and growth of an individual cell.

Cellular automata are a well-known formal context for distributed modelling. The cellular automata is a lattice of sites (cells), each with a finite set of possible values. The values of the cells evolve synchronously in discrete time steps according to identical rules. The value of a particular cell is determined by the cell transition function which maps the state of the cell and all its predefined neighbours to a new state of the cell.

The simple and formally precise concept of the cell transition function which specifies how the state of a cell depends on the state of its neighbours is also the source of disadvantage of the cellular automata. This is because it is sometimes very difficult and awkward to specify a transition function of automata for modelling otherwise simple behaviour, like, for example, movements or collisions, and in such cases a concept of specifying how the cell affects its neighbour cells seems to be more natural. This concept has been realized in the abstract universe, another universal medium for distributed modelling (Jędruch and Sampson, 1987; Jędruch and Barski, 1990), which is especially convenient when the movement of elements is inherent in the behaviour of a modelled system.

The universe is a system of entities in a two-dimensional space. The entities move and collide according to rules like those of classical mechanics, and at a higher level of organization they interact between themselves according to functions encoded in them. A computer program (written in Turbo-Pascal language) can simulate the evolution of the universe starting from any initial configuration of the entities thus allowing us to model various systems. The universe has already been used for simulation of various physical systems as diffusion process, cluster formation, chemical reaction kinetics, predator-prey systems, and growth of various complex structures (for some of them see Jędruch and Barski, 1990; Jędruch, 1993a; 1993b).

After presenting briefly the universe and its computer implementation, the paper discusses the results of a few computer simulation experiments illustrating possible ways of using distributed modelling in the field of cell population dynamics.

## 2. The Universe

The universe is defined over a two-dimensional tessellation of identical squares. A square may be empty or contain any number of elements belonging to the set $E = A \cup \{f\}$, $A = \{0,1\}$. Elements $A$ are called atoms and $f$ — photons. Atoms occupying a square form a particle, whose properties are fully determined by its velocity and the one-dimensional sequence of its constituent atoms. The permanence of the particle depends on its bond energy; this is what suffices to disintegrate the particle into single atoms. The bond energy of the particle is the sum of the bond energies between its constituent atoms. Particles in adjacent squares can bond together to form a complex of particles.

All the transformations in the universe obey the momentum and energy conservation laws and are synchronized by a discrete clock.

Atoms are permanent elements of the universe; they are not created nor annihilated during its evolution. Photons are temporary elements; they transport energy and are created by reactions which dissipate energy.

### 2.1. Movements and Collisions

During each time step, particles and complexes can move by jumping randomly to adjoining squares in the $x$ and $y$ directions with probabilities:

$$P_x = \begin{cases} |v_x/s| & \text{if } v \leq s \\ |v_x/v| & \text{otherwise} \end{cases}, \qquad P_y = \begin{cases} |v_y/s| & \text{if } v \leq s \\ |v_y/v| & \text{otherwise} \end{cases} \tag{1}$$

where $s$ is a constant, $v = \sqrt{v_x^2 + v_y^2}$, $v_x$ and $v_y$ denote the velocities of the particle in $x$ and $y$ directions, respectively.

Photons can move by jumping to adjoining squares in the $x$ and $y$ directions with probabilities:

$$P_{fx} = |\cos\varphi|, \qquad P_{fy} = |\sin\varphi| \tag{2}$$

where $\varphi$ is a photon direction of movement chosen randomly at the moment of the photon creation.

When a particle attempts to occupy the square already occupied by another particle or when a photon jumps into the square occupied by a particle, a collision occurs, after which the new states of particles and photons are evaluated.

There are four types of collisions: the elastic and inelastic collision of two particles, and the elastic and inelastic collision of a particle and a photon. The latter collision is further classified into six subtypes: rebounding of the particle hit by the photon from an adjoining particle; setting bond between the hit particle and an adjoining particle, resetting bond; changing the order of atoms in the hit particle; absorption of the adjoining particle by the hit particle; splitting of the hit particle into two particles. The type and particulars of reaction are chosen randomly.

### 2.2. Functional Interactions

In another class of interactions the particles are capable of inducing transformations in the space around them according to functions encoded in them. The description of the function of the particle is contained in its string of atoms, which is interpreted as a program written in a specially defined language (Jędruch and Barski, 1990). The function contained in the particle can recognize particular structures of particles and complexes, and transform them by moving them, changing bonds between them, splitting them, concatenating them, or changing the order of atoms in them. Using these transformations the function of one particle can modify the function of other particles. The area of the functional activity of a particle is a square region (called $\Omega$) centred around the particle. In a given time step, the functions of particles are activated in a randomly chosen succession; a function activated later may affect the area which was transformed by functions activated earlier. Although each particle contains a function, some functions are nonsense and are not realized.

### 2.3. Computer Implementation

A computer program simulating the universe has been written in Turbo-Pascal language. The simulation program first loads the initial state of the universe from a disk file, and then runs in time steps. In each time step there are realized movements of photons and their collisions with particles, movements and collisions of particles, and functions of particles. During the simulation, a graphic pattern of the universe is displayed on the screen. After the simulation is finished, the resulting state of the universe is stored back on the disk, so that the simulation could be resumed from the new state.

Besides the main simulation program, several tools have been designed to facilitate preparation of initial states of the universe and observation of some of its parameters.

## 3. Simulation Experiments

A few computer simulation experiments are presented, showing the universe potentialities for modelling various processes in the area of cell population dynamics. Models of chemical reaction kinetics, cluster formation, and growth of a structure similar to a cell wall are discussed.

In all experiments presented the initial velocities of the particles were chosen randomly from the range $(-3, 3)$, independently in the $x$ and $y$ directions, and the constant $s$ in formula (1) was set to be equal to 5.

### 3.1. Chemical Reaction Kinetics

The universe makes possible various approaches to the modelling of chemical reaction kinetics, and two of them are presented below. These models can also be interpreted as models of cell population dynamics.

In the first experiment the reaction $A + B \rightarrow AB$ was modelled. In the universe there were particles referred to as $A$ (consisting of atom 0) and $B$ (atom 1) (thus

both containing nonsense functions) and particles $P$ containing valid functions which bond two free, adjacent particles $A$ and $B$.

The size of the universe was set to be 320 by 174 squares, and the size of particle functional activity area $\Omega$ was set to be equal to 5. The initial state of the universe consisted of $[A]_0 = 1500$, $[B]_0 = 1500$, and $[P]_0 = 20, 50, 100, 200, 500$, where $[\cdot]_0$ denotes the initial value. For each value of $[P]_0$ the experiment was run for 1000 time steps.

As a mathematical model of the reaction

$$A + B \xrightarrow{k} AB \tag{3}$$

the following equation was taken (using the Law of Mass Action (Murray 1989, p.110))

$$\frac{\mathrm{d}[AB]}{\mathrm{d}t} = k\left([A]_0 - [AB]\right)\left([B]_0 - [AB]\right) \tag{4}$$

with initial condition $[AB]_0 = 0$, where $k$ is the rate constant. Assuming $[A]_0 = [B]_0$ the solution to equation (4) is

$$[AB] = \frac{[A]_0^2 kt}{[A]_0 kt + 1} \tag{5}$$

To fit solution (5) to the experimental data it has been assumed that $k = k_0[P]_0$. Minimizing the square criterion for the number of complexes $[AB]$ with respect to coefficient $k_0$ gives

$$\min_{k_0} \sum_{\substack{[P]_0=20,50,\\ 100,200,500}} \sum_{i=1}^{1000} \left([AB]_{[P]_0 d}(i) - [AB]_{[P]_0 e}(i)\right)^2 = 1.03 \times 10^6 \tag{6}$$

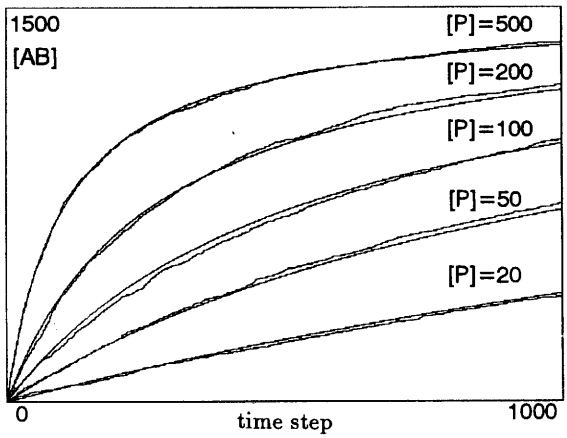
for $k_0 = 1.25 \times 10^{-8}$, where $[AB]_{[P]_0 d}(i)$ and $[AB]_{[P]_0 e}(i)$ denote the number of complexes $AB$ at the time step $i$, given by equation (5) and obtained experimentally, for the number of particles $[P]_0$. Figure 1(a) shows the number of complexes $AB$ obtained from (5) for $k_0 = 1.25 \times 10^{-8}$, and the one obtained experimentally.

In the second experiment the enzymatic reaction $A+E \rightarrow AE$, $AE+B \rightarrow C+E$ was modelled. In the universe there were particles $A$ (consisting of atom 0) and $B$ (atom 1) and particles $E$ containing valid functions. The particle $E$ bonded to itself the free particle $A$, and in the next time step concatenated the particle $B$ with the particle $A$ creating the particle $C$, which then detached from itself.

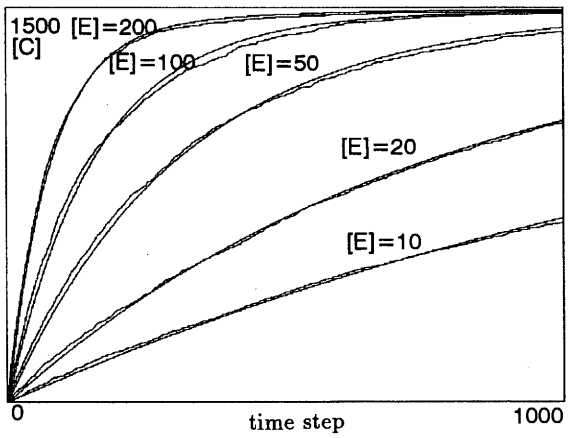
The size of the universe was set to be 320 by 174 squares, and the size of $\Omega$ was set to be 5. The initial state of the universe consisted of $[A]_0 = 1500$, $[B]_0 = 1500$, $[C]_0 = 0$ and $[E]_0 = 10, 20, 50, 100, 200$. For each value of $[E]_0$ the experiment was run for 1000 time steps.

As a mathematical model of the reaction

$$A + E \xrightarrow{k_1} AE, \qquad AE + B \xrightarrow{k_2} C + E \tag{7}$$




a)




b)

Fig. 1. Modelling chemical reaction kinetics. (a) The reaction $A + B \rightarrow AB$. Experimental and theoretical curves representing the number of particles $AB$ for various numbers of particles $P$. (b) The enzymatic reaction $A + E \rightarrow AE$, $AE + B \rightarrow C + E$. Experimental and theoretical curves representing the number of particles $C$ for various numbers of particles $E$.

the following equations were taken:

$$\begin{aligned} \frac{\mathrm{d}[C]}{\mathrm{d}t} &= k_2[AE][B] \\ \frac{\mathrm{d}[AE]}{\mathrm{d}t} &= k_1[A][E] - k_2[AE][B] \end{aligned} \tag{8}$$

where $[B] + [C] = [B]_0$, $[A] + [AE] + [C] = [A]_0$, $[E] + [AE] = [E]_0$.

To fit the numerical solution to equations (8) to the experimental data it has been assumed that $k_1 = k_2 = k$. Minimizing the square criterion for the number of particles $[C]$ with respect to the coefficient $k$ gives

$$\min_k \sum_{\substack{[E]_0=10,20,\\ 50,100,200}} \sum_{i=1}^{1000} \left([C]_{[E]_0 d}(i) - [C]_{[E]_0 e}(i)\right)^2 = 1.32 \times 10^6 \tag{9}$$

for $k = 1.26 \times 10^{-4}$, where $[C]_{[E]_0 d}(i)$ and $[C]_{[E]_0 e}(i)$ denote the numbers of particles $C$ at the time step $i$, obtained from numerical solution of equations (8) and those obtained experimentally, for the number of particles $[E]_0$. Figure 1(b) shows the numbers of particles $C$ obtained from equations (8) for $k = 1.26 \times 10^{-4}$, and those obtained experimentally.

### 3.2. Cluster Formation

The universe could be very useful for modelling various processes of cluster formation. In the experiment described in (Seledec, 1993) the universe in its initial state contained a complex of four particles referred to $Z$ being a seed of the growing structure of 2000 particles, $M$, being a material bonded to the seed, and 100 particles, $P$, containing functions bonding free particles $M$ with adjacent particles $Z$ or other particles $M$ if the latter belong to the complex. The particles $Z$ and $M$ contained nonsense functions. The size of the universe was set to be 160 by 160 squares, whereas the size of $\Omega$ was set to be equal to 3. The growth of the fractal-like structure can be seen in Fig. 2.

### 3.3. Growth of a Cell Wall

In the experiment the system of particles makes the growth of a structure similar to a cell wall. The size of the universe was set to be 320 by 320 squares, and the size of $\Omega$ was set to be equal to 17.

The initial state of the universe consisted of:

1. The cell wall (62 particles).
2. Outside the cell there were particles which were used as building materials (1500 particles) and particles which served as sources of energy (2500 particles).
3. Inside the cell there were eight types of particles containing valid functions (32 particles) which directly build up the wall, transport the building materials and energy rich particles through the wall into the cell, and remove from the cell the particles whose energy was used.

The initial state of the universe and the state after 6500 steps is shown in Fig. 3. During simulation, the particles inside the cell, while moving and colliding randomly, kept gradually enlarging the cell's wall. The similar experiment with a lower number of particles and smaller size of the universe can be found in (Jędruch and Barski, 1990).

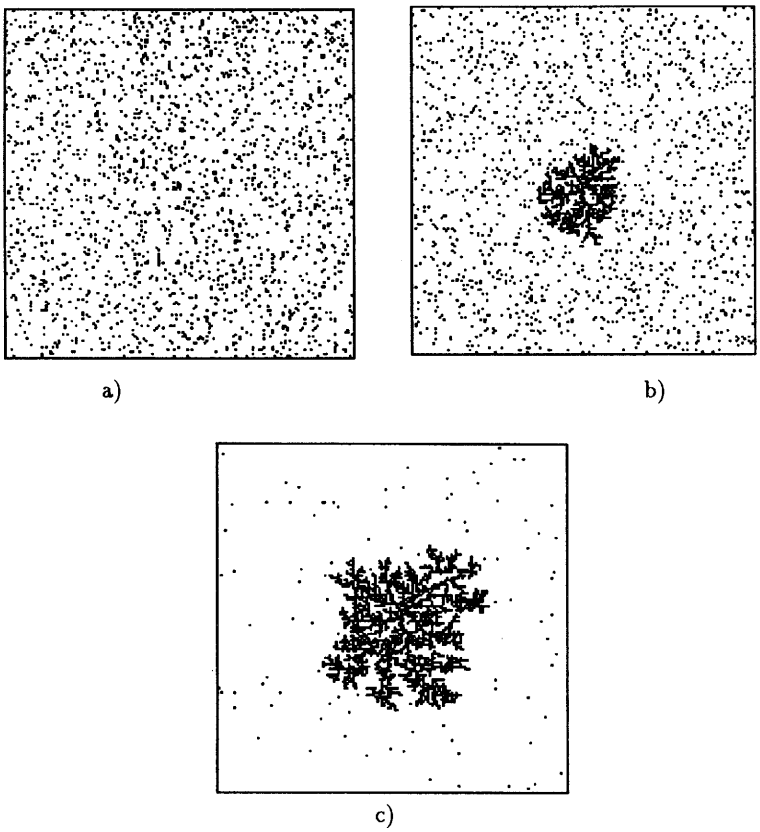
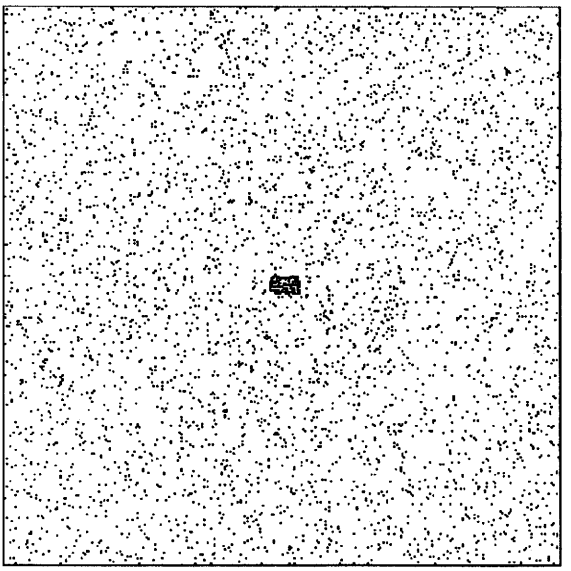



Fig. 2. Development of the cluster. (a) The initial state of the universe, and (b), (c) the states after 600 and 3000 time steps, respectively.

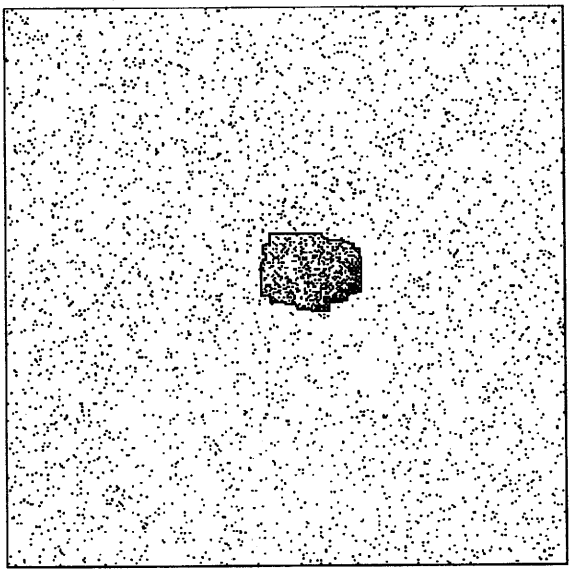
## 4. Concluding Remarks

An abstract universe — a universal simulation environment for distributed modelling of physical systems has been discussed and a few simulation experiments have been presented, to illustrate possible ways of using the universe for modelling of cell population dynamics.

The experiments with chemical reaction kinetics show that the physical phenomena described by non-linear equations can be effectively modelled using the distributed approach with a relatively small number of elements. The experiments with cluster formations and growth of the structure similar to a cell wall illustrate the effects of cooperative behaviour of simple elements leading to the development of complex structures. All the experiments presented here show another feature offered by the distributed models — they can mimic nature by the "first principles" and without using any averaging; they just operate on a finite number of elements.



a)



b)

Fig. 3. Build up of the wall. (a) The initial state of the universe, and (b) the state after 6500 time steps.

It appears that the results obtained demonstrate an attractive approach to modelling various cell population systems and the growing speed of computers will make this approach even more attractive.

## References

Jędruch W. and Sampson J.R. (1987): *A universe for molecular modeling of self-replication.* — Bio-Systems, v.20, No.3, pp.329–340.

Jędruch W. and Barski M. (1990): *Experiments with a universe for molecular modelling of biological processes.* — BioSystems, v.24, No.1, pp.99–117.

Jędruch W. (1993a): *Distributed modelling of a predator-prey system.* — Proc. 3rd Int. Conf. *Mathematical Population Dynamics*, Pau, France (in press).

Jędruch W. (1993b): *An abstract universe for distributed modelling of complex systems.* — Proc. 7th Int. Conf. *System, Modelling, Control*, Zakopane, Poland, Technical University of Łódź, v.1, pp.213–218.

Langton C.G. (1989): *Artificial life.* — In: Artificial life, (C.G. Langton, Ed.), Proc. Interdisciplinary Workshop on *Synthesis and Simulation of Living Systems*, Los Alamos, New Mexico, Sept., 1987, Addison-Wesley: Redwood City, Cal.

Murray J.D. (1989): *Mathematical Biology.* — Berlin: Springer-Verlag.

Seledec P. (1993): *Distributed models to develop complex structures.* — M.Sc. Thesis, Faculty of Electronics, Technical University of Gdańsk, Poland, (in Polish).

Toffoli T. (1984): *Cellular automata as an alternative to differential equations in modelling physics.* — In: Cellular Automata (D. Farmer, T. Toffoli and S. Wolfram, Eds.), Proc. Interdisciplinary Workshop, Los Alamos, New Mexico, USA, March 7–11, 1983, Physica 10D, pp.117–127.