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POPULATION MODEL BASED ON CELLS WITH INTERNAL DYNAMICS

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Abstract

A model of a population is constructed by bringing together individual model organisms (cells) which have explicit internal dynamics. An attempt is made to preserve analyzability of the relatively complex model by describing the nonlinear dynamics of each cell by a set of piece-wise linear equations. In the simplest case of three linear pieces, a population with inherent oscillations in the number of cells as a function of time is obtained. A proposal is made to approximate realistic internal dynamics of selected biological features by introducing the appropriate number of linear patches, and to simulate realistic populations in this way. Another extension of the model, the description of interactions between cells through released metabolites, is used to represent the situation of a chemostat.

1. INTRODUCTION

Biological phenomena can be presented as a hierarchy: biochemical processes occuring inside organisms standing at the bottom of the hierarchy, ecological interactions between organisms forming the next level of organization, and finally evolutionary phenomena involving populations of organisms constituting the uppermost level. Of course, additional levels of organization can be distinguished, particularly in multicellular organisms, such as cells, tissues, and organs, but our interest is in a novel situation requiring a minimum number of hierarchical levels, and so we will content ourselves with the above mentioned three levels.

Biochemical processes occurring in cells have been studied for a long time, initially mostly with regard to molecular structure and constitution, but have now progressed to a point where their dynamical nature is acknowledged and has begun to be characterized. In some cases sufficient experimental information has become available to define useful chemical kinetics models.

Ecological and evolutionary phenomena also have been intensively investigated. Considerable success has been achieved in describing food webbs, and the stability of populations in certain environments is well understood. The realization that deterministic, aggregate variable (e.g. population numbers, food or spatial resources) models cannot account for many observations has led to the introduction of age structured populations, as well as the use of distributed environment models, often in a probabilistic or statistical mechanics context. These approaches have even led to

quantitative success in some issues of population genetics, but models of more general evolutionary processes have proved unsatisfactory. In almost all of the above cases the basic structures being postulated have been purely static ones, even when internal structure has been introduced. (See: Murray, 1994; Lundberg and Fryxel, 1995; Zimov et al., 1995.) An exception to this may be found in some so called 'artificial life' models (see Taylor et al., 1989; Hraber, Jones and Forrest, 1996; Hraber and Milne, 1997; Schmitz and Booth, 1997). In such models the entities being modeled are represented by computer subprograms. Because one must commit to a specific set of parameters in each run of such a model, it becomes very time consuming to derive general consclusions. Further, because computer programs do not lend themselves to most modes of analysis, usually it is no easier to understand the behavior of such a model than the behavior of the natural system itself. One thing is clearly reinforced by these models however: the internal structure of the organisms clearly matters in both ecological and evolutionary processes.

In this paper an explanatory model for ecological phenomena incorporating internal dynamics of individual organisms is introduced. The model resembles artificial life models in its scope and in using a computer, but also offers increased opportunities for analysis.

2. DEFINITION OF THE MODEL

2.1 Structure of the model. The model being introduced here is based on dynamical models for individual organisms, which will be refered to as cells. Each cell in the model is considered to be an open system. A population is made up of a collection of individual cells embedded in a common environment. The scheme of interactions between individual cells and the common environment is presented in Fig.1. The number of individual cells in the model is dependent on the amount of environmental resources and can vary with time.

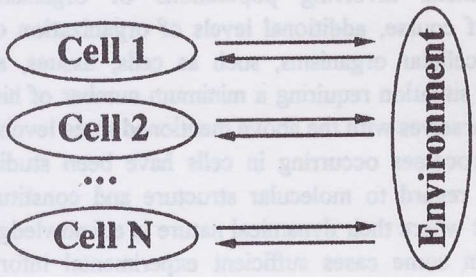

Fig. 1. Scheme of interactions of cells with the common environment

2.2 Model of a cell. In modeling an individual cell we would like to incorporate the main important characteristics of a living system. A cell is represented as an open dynamical system. This allows for the intake of food, for growth, and for cell division or death, all the processes being dependent on the internal state. Additionally, in more

complicated versions of the model, the cell can release metabolites. Two types of state variables are introduced in the model of a cell: genotypic state variables and phenotypic state variables, differing in the way they are influenced by the environment. The phenotypic state is directly influenced by environment but the genotypic state can be influenced by the environment only through the phenotypic state. More specifically, we give the cell model in terms of state variables, parameters and input variables:

$$l(t) = \{x(t), A, B, H, L_D, L_N, u(t)\}, \tag{1}$$

where $x = \begin{pmatrix} x_g \\ x_f \end{pmatrix}$ – cell state vector, x_g – the genotypic state, – x_f – the phenotypic state, $A = \begin{pmatrix} a_{gg} & a_{gf} \\ a_{fg} & a_{ff} \end{pmatrix}$, $B = \begin{pmatrix} 0 \\ b \end{pmatrix}$, $H = \begin{pmatrix} h_g \\ h_f \end{pmatrix}$, L_D, L_N – cell dynamics parameters, $u(t) > 0$ – cell input variable, describing the influence of the environment.

The nonlinear dynamics of the cell $l(t)$ is represented by piece-wise linear functions over the state space. At least three linear parts are required: one for cell growth, the other for cell division and the third for cell death. Partition of the cell state space is shown in Fig. 2. The most extensive is the growth region. Dynamics of a cell in the growth region is described by ordinary differential equations, while division and death happen when the cell reaches boundaries of the growth region, the division and death being described by difference equations:

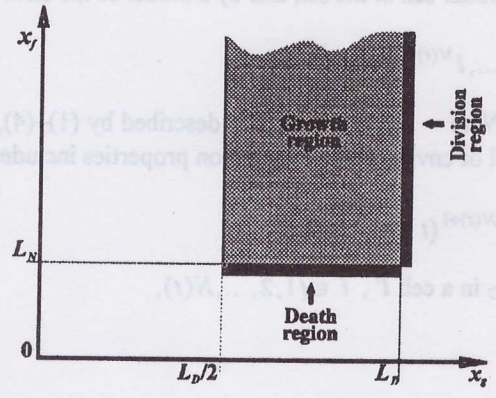

Fig. 2. Regions of the cell state space. Growth occurs on the rectangular patch, bounded by lines $x_g = L_D/2$, $x_g = L_D$ and $x_f = L_N$. Division and death regions are degenerate patches $x_g = L_D$ and $x_f = L_N$.

1. Growth

$$\frac{dx}{dt} = Ax(t) + Bu(t) + H; \tag{2}$$

valid when $L_D / 2 \le x_g(t) < L_D$, $x_f(t) > L_N$;

2. Division

$$x(t+\varepsilon) = x(t)/2,\ \varepsilon \to 0; \tag{3}$$

valid when $x_g(t) = L_D$;

3. Death

$$x(t+\varepsilon) = 0,\ \varepsilon \to 0; \tag{4}$$

valid when $x_f(t) = L_N$.

A cell cycle begins on the line $x_g = L_D/2$. The cell can divide on reaching $x_g = L_D$, or die upon reaching $x_f = L_N$. Two scenarios of cell death can take place: 1) the cell can reach the death boundary in the course of its growth process, or 2) the cell can crosses the death boundary at the moment of division. Leaving the growth region through the boundary $x_g = L_D$ is forbidden by an appropriate choice of the parameters A, B, H, L_D, L_N. The fact that genotypic dynamics is independent of the environmental influence $u(t)$ causes the steady points of the linear growth equation (2) to group on a line in state space.

2.3 A population model. The population is modeled as a set of cells, the set emerging in the process of division and death of individual cells. The population is specified by models for each individual cell in the set, and by a model of the environment:

$$P(t) = \left\{ l^1(t), l^2(t), \ldots, l^{N(t)}(t), E(t) \right\}, \tag{5}$$

where $l^i(t)$, $i = 1, \ldots N(t)$ – individual cells as described by (1)–(4), $N(t)$ – number of cells; $E(t)$ – a model of environment. Population properties include cell division

$$l^i(t) \to \left\{ l^i(t+\varepsilon), l^{N(t)+1}(t+\varepsilon) \right\}\ \varepsilon \to 0; \tag{6}$$

valid when $x_g^i(t) = L_D$ in a cell l^i, $i \in \{1, 2, \ldots, N(t)\}$,

and death.

$$l^j(t) \to \varnothing,\ \varepsilon \to 0; \tag{7}$$

valid when $x_f^j(t) = L_N$ in a cell l^j, $j \in \{1, 2, \ldots, N(t)\}$.

The environment $E(t)$ is represented by giving a global autonomous dynamics and a mechanism for division of resources between cells:

$$E(t) = \left\{U(t), N(t), u^1(t), u^2(t), \ldots, u^{N(t)}(t)\right\}, \tag{8}$$

where $U(t)>0$ – global environmental resources, $N(t)$ – number of cells in a population (5), $u^i(t)$ – an amount of resources allocated to the cell $l^i(t)$.

Division of environmental resources is specified by expressions of the form

$$u^i(t) = F_i\left(U(t), N(t)\right), \qquad i=1,2,\ldots,N(t), \tag{9}$$

where F is a stochastic function. Partitioning of the resources $u^i(t)$ should satisfy the balance equation

$$E\left[u^i(t)\right] = \frac{U(t)}{N(t)}, \tag{10}$$

where E - a symbol for the mean.

3. PROPERTIES OF THE MODEL

3.1 Concentration of cells. Let us analyze the case when an individual cell displays stable growth dynamics (2). In this case, limitation of a population by environmental resources is possible in the model. At first we will apply equal division of environmental resources $U(t) \equiv U$:

$$u^i(t) = \frac{U}{N(t)}, \quad i=1,2,\ldots,N(t). \tag{11}$$

In the case of equal division of resources, the cells tend to group on the same trajectory because of attraction to the common stable point in the phenotypic direction. When all the cells enter the same trajectory, additional genotypic states no longer can be created. By this time some of the genotypic states become extinct through cell death, and after a period of time the whole population becomes synchronized in the genotypic direction, as well as concentrated in the phenotypic direction. When these concentrated cells divide, the carrying capacity of the environment is exceeded, and all the cells in the population die out at the same moment. Even though the described scenario will be realistic from a biological point of view only under special circumstances, in this scenario, if additionally the growth matrix is diagonal or lower triangular, the dependence of population properties on parameters of individual cells can be estimated by means of analysis (see Tamošiūnaitė and Vaišnys, 1997). Computer experiments allow to find out which of the results of the analysis hold in the case of a general growth matrix.

3.2 Stabilization of population by dispersal of inputs. For the population to persist, an environmental model with dispersal of cell inputs (and cell states, consequently) is required. When applying inputs $u^i(t)$ from the uniform distribution over the range $[0,2U/N(t)]$, cell states become dispersed widely enough for a population to persist as long as desired. An example of a time series of such a persistent population is given in Fig. 3.

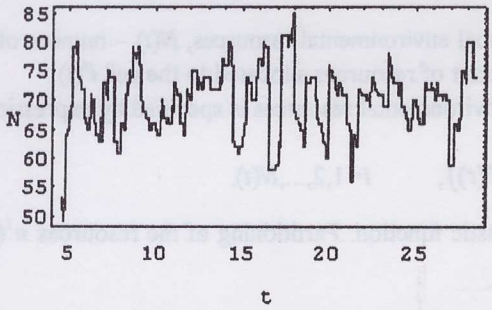

Fig 3. Time series of a persistent population. Parameters of an individual cell: $a_{gg} = -1$; $a_{gf} = 0$; $a_{fg} = -0.2$; $a_{ff} = -1.1$. Amount of environmental resources $U = 200$. Inputs u^i are taken from uniform distribution in the range $[0,2U/N(t)]$.

3.3 Oscillations in population. After persistency of a population has been achieved, some amount of synchronization of the genotypic states in cells can nevertheless be observed. The synchronization is represented by oscillations in the time series of the size of a population. The synchronization, and oscillations, are caused by introduction of the selected type of internal dynamics of cells into the model.

The phenotypic state of a cell is directly influenced by the amount of available resources. The phenotypic state of the cell also represents some sort of a record about the amount of resources consumed in the past. In the proposed model the mean amount of resources available to an individual cell depends on the number of cells in a population. When the number of cells increases, the phenotypic states of all cells will tend to approach the death boundary. The cells with the lowest state values will die, crossing the death boundary, and leave a greater amount of resources to the surviving cells. Nevertheless, even when the number of cells in a population has dropped down to the carrying capacity of the environment, the death of some cells which are near their division point is unavoidable because of their low phenotypic state values, acquired in the past. When a considerable number of cells, on reaching the division boundary, die immediately after division an empty range of genotypic states forms. The existing cells concentrate in the remainder of the range. Though distribution of inputs tends to increase the dispersal of genotypic states, the process is too slow to fill the existing gaps before new gaps appear.

3.4 Dynamics induced by several linear growth patches. Instead of having a single integral growth region, which we have investigated until now, several linear patches can be introduced inside the region. By increasing the number of linear patches, any kind of growth dynamics can be approximated, for example, to match empirical observations. While such a model would be more difficult to analyze, the desirable property of analyzability should be retained to a useful extent as long as a small number of linear patches is involved.

The advantages gained by the introduction of several growth patches is demonstrated by the version of the model with two growth patches: stable in the

region of the higher values of the phenotypic state and unstable in the region of the lower values of the phenotypic state (see Fig. 4). In this case, minor environmental fluctuations can preserve the population persistently, in contrast to the single growth patch case, when an unrealistically wide range of input dispersal was required. The unstable part in the two patch case is responsible for dispersal of cells, while the stable part provides a limitation of population size (see Tamošiūnaitė and Vaišnys, 1997).

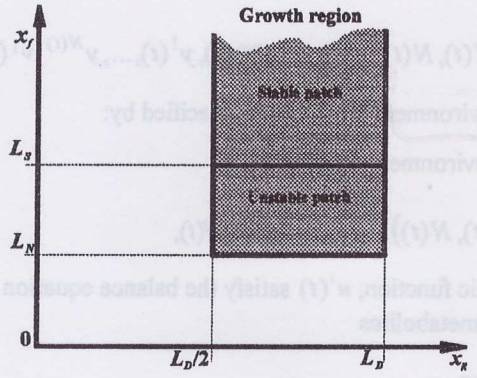

Fig. 4. partition of the cell growth region in the case of two growth patches.

4. ADDITIONAL PROPERTIES OF A MODEL WITH INTERACTIONS

4.1 Definition of interactions. The proposed model can be readily extended by introducing interactions between cells through cell produced metabolites. By introducing accumulation of metabolites in the cell environment, and washout from the environment, a model describing the operation of a chemostat can be achieved.

Let us extend the model of a cell (1), by introducing some rate of metabolite excretion $y(t)$, amount of metabolites in the environment of the cell $v(t)$, and additional parameters C and D to describe the interactions:

$$l(t) = \{x(t), y(t), A, B, H, C, D, L_D, L_N, u(t), v(t)\}, \tag{12}$$

where $D = \begin{pmatrix} 0 \\ d \end{pmatrix}$ – a vector of parameters defining metabolite influence upon the cell,

$C = \begin{pmatrix} 0 & c \end{pmatrix}$ – vector of parameters defining the rate of metabolite excretion.

Let us change the growth equation (2) by introducing the influence of environmental metabolites $v(t)$ on the cell state,

$$\frac{dx}{dt} = Ax(t) + Bu(t) + Dv(t) + H. \tag{13}$$

Let us also describe the rate of metabolite production $y(t)$ by the equation:

$$y(t) = Cx(t). \tag{14}$$

The specification of the environment $E(t)$ (8) will now be extended by introducing the rates of metabolite production by individual cells $y^i(t)$ (i=1,2,...,$N(t)$), the amount of metabolites accumulated in the environment by $V(t)$, and the distribution of the amount $v^i(t)$ between cells, as well as the washout rate s:

$$E(t) = \left\{U(t), V(t), N(t), u^1(t), \ldots, u^{N(t)}(t), y^1(t), \ldots, y^{N(t)}, v^1(t), \ldots, v^{N(t)}(t), s\right\}, \tag{15}$$

Properties of the environment $E(t)$ will be specified by:

1. Distribution of environmental resources

$$u^i(t) = F_i\left(U(t), N(t)\right), \qquad i=1,2,\ldots,N(t), \tag{16}$$

where F - a stochastic function; $u^i(t)$ satisfy the balance equation (10);

2. Accumulation of metabolites

$$\frac{dV}{dt} = -sV + \sum_{i=1}^{N(t)} y^i(t); \tag{17}$$

3. Distribution of accumulated metabolites

$$v^i(t) = F'_i\left(V(t), N(t)\right), \qquad i=1,2,\ldots,N(t), \tag{18}$$

where F' - a stochastic function. Amounts $v^i(t)$ should satisfy balance equations in analogy with the amounts of resources $u^i(t)$:

$$E\left[v^i(t)\right] = \frac{V(t)}{N(t)}, \tag{19}$$

Under the assumption that resources and metabolites are distributed according to the same principle, the functions F and F' should be identical.

4.2 Effect of interactions on population properties. With this model it is possible to obtain a realistic relationship between the mean number of cells and the mean amount of metabolites in the simulated environment (the mean evaluated throughout time) and the washout rate (see Fig. 5). The curves are drawn according to computer simulation results. Zero valued gaps in the curves, occurring at high values of washout, correspond to events of population extinction and show the decreased stability of a population under conditions of intensive washout.

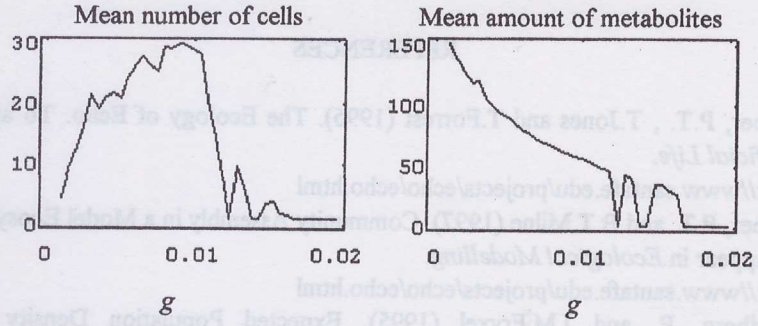

Fig. 5. Relation of the number of cells in a population and the amount of metabolites in the population environment to the rate of washout $g=\Delta t \times s$, where Δt denotes the step of integration. Fixed parameters $a_{gg} = -1.$; $a_{gf} = 0.05$; $a_{fg} = -0.2$; $a_{ff} = -1.1$; $U = 170.5$; $CD = 0.01$; $\Delta t = 0.01$. Inputs of resources and metabolites for individual cells are chosen independently from the uniform distribution over the range $[0,2U/N(t)]$ at every step of integration of length Δt.

Interactions of cells through the produced metabolites increase oscillations in the number of cells in a population in some parameter ranges. These additional oscillations produced by the introduction of interactions do not appear to increase the probability of population extinction. This model with interactions may be applied to the exploration of the phenomena of homeokinesis in a chemostat.

5. CONCLUSIONS

A model for a population of cells (organisms), in which each of the cells has an internal dynamics, is introduced in this paper. The nonlinear internal dynamics of the cells is described by piece-wise linear differential equations. The population behavior emerges as the result of interactions between individual cells through a common environment. In the case when environmental resources are equally divided among all the cells in a population, the cells concentrate at a single point in cell state space. A persistent population, with oscillations in the number of cells as a function of time as a characteristic feature, can be achieved by introducing probabilistic dispersal in environmental resources.

The proposed model may not seem to be biologically realistic because the postulated linear cell growth dynamics may appear too simple. Note however, that once different regions of cell state space are described by different linear functions, the overall dynamical model becomes nonlinear. In this way, any desired features of more realistic internal dynamics can be approximated. Additionally, interactions of cells through produced metabolites can be introduced into the model. With these extensions to the original simple model it is possible to model the essential properties and behavior of not only a chemostat but also of more complex biological populations.

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