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On the mathematical synthesis of physiological and
behavioural mechanisms and population dynamics

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A concise description of a mathematical framework for the synthesis of physiological ecology and population dynamics is presented.

1. INTRODUCTION

When investigating the biological world we can concentrate on different levels of organization. For instance, we can look at *individual organisms* and try to understand their *life cycle* and the *physiological processes* that are essential for their functioning. Or we can look at *populations* of such organisms and try to understand or even predict how *numbers* change in the course of time.

In reality these levels are strongly coupled but theoretical as well as experimental studies in ecology and cell kinetics tend to neglect the interplay more or less, with the work of STREIFER (1974), BELL & ANDERSON (1967), AUSLANDER, OSTER & HUFFAKER (1974), FREDRICKSON, RAMKRISHNA & TSUCHIYA (1967) as early exceptions worth mentioning. A recent attempt to revive the spirit of these older papers and to bridge the gap between the individual and the population level by means of a special class of mathematical models goes under the heading "Dynamics of Structured Populations", where sometimes the adverb "physiologically" is used to emphasize the difference with models incorporating spatial structure (METZ & DIEKMANN, to appear). In a collective effort we try to study interesting examples in detail, to unravel the general mathematical structure of the class of models and to fit the corresponding class of partial functional differential equations into the framework of dynamical systems theory. This paper is a kind of progress report on work done by Hans Metz, Henk Heijmans, Mats Gyllenberg, Horst Thieme and myself, strongly stimulated by and partly in collaboration with Tom Aldenberg, Frank van den Bosch, Bas Kooijman, Roger Nisbet, André de Roos, Mous Sabelis and John Tyson. In addition, I sketch some lines to the future. This paper, with its concise and, at times, not very precise formulation, is meant as an invitation to read METZ & DIEKMANN (to appear), HEIJMANS (1985, to appear) and CLÉMENT et al. (in preparation).

2. MODELLING

The following is a recipe for the formulation of a structured population model:

(i) Distinguish individuals from one another according to relevant variables. That is, choose finitely many *i-state variables* (*i*- for individual) which, by assumption, contain sufficient information about the past of an individual to fix its future, as far as it concerns population dynamically relevant events. EXAMPLES of *i*-state variables: age, size, energy reserves, amount of foliage.

(ii) Genuine modelling: specify and describe (mathematically) the *processes* which change the *i*-state and those which lead to the creation or destruction of individuals. The smooth "change" processes describe the trajectories of individuals in the *i*-state space and we usually assume that these are *deterministic* (i.e. identical for all individuals in a given *i*-state) and described by an ordinary differential equation. EXAMPLES: aging, growth. The "creation-destruction" (including jump) processes are usually *stochastic* (some die some don't) but we will always assume that numbers are so large that we can describe these *chance* processes in terms of *rates* (like most of the time in chemistry and deterministic population dynamics). EXAMPLES: fission, removal from a chemostat by overflow. (Of course steps (i) and (ii) are not independent and one may actually go repeatedly back and forth between them before ending up with a satisfactory description of the *i*-dynamics).

(iii) Introduce a density function $n = n(t,x)$, t = time, x = *i*-state, to describe the *p-state* (*p*- for population) and do the necessary *bookkeeping* to derive how the *i*-processes can be expressed at the *p*-level. So $\int_\omega n(t,x)dx$ = number of individuals at time t with *i*-state in ω, where ω is any (measurable) subset of the *i*-state space. The ideal is, of course, to be able to compute $n(t,.)$ for $t > t_0$ when $n(t_0,.)$ is given. In finite time intervals all the different processes are interweaved in an intricate manner and this complicates the bookkeeping to such an extent that it becomes impossible to define the mappings $n(t_0,.) \to n(t,.)$ directly. The old solution to this problem is to take limits, i.e. compare $n(t_0 + \delta,.)$ and $n(t_0,.)$ and let $\delta \downarrow 0$ to derive a partial *differential equation*. In small time intervals there will be hardly any compound events and in the limit these can be neglected all together. We end up with a partial differential equation which compactly summarizes the influence of the processes at the individual level on the population as a whole and which is based on the requirement that our bookkeeping should be correct.

EXAMPLE: Let cells be characterized by their size x. Assume that reproduction occurs through asymmetric division into a part of fixed size x_0 (the daughter) and a part of size $x - x_0$ (the mother). The budding yeast *Saccharomyces cerevisiae* may serve as an example. Let $g(x)$ denote the growth rate of individual cells and $b(x)$ the probability per unit of time that a cell of size x divides. The balance law describing the time-evolution of the size- distribution is

$$\frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}(g(x)n(t,x)) = -b(x)n(t,x) + b(x+x_0)n(t,x+x_0)$$

$$g(x_0)n(t,x_0) = \int_0^\infty b(\xi)n(t,\xi)d\xi$$

GENERAL STRUCTURE:

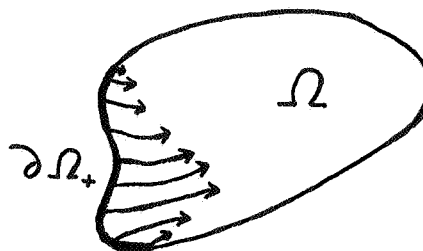$\frac{\partial n}{\partial t}$ + divergence (velocity n) = sources - sinks

ν . velocity $n|_{\partial\Omega_+}$ = source

Ω = *i*-state space

ν = inward normal to $\partial\Omega$

$\partial\Omega_+$ = part of $\partial\Omega$ at which ν. velocity >0, i.e. characteristics enter Ω

EXPLANATION: If we denote the i-variable by x then the trajectories of individuals are governed by $\dfrac{dx}{dt} =$ velocity. In mathematical terminology these trajectories are (the projections on Ω of) the characteristics. The source terms correspond to the "creation" processes and the sink terms to the "destruction" processes.

If we apply the above scheme to e.g. unicellular organisms (living, say, in a chemostat) we encounter a serious problem which is somewhat hidden in the general formulation: if we would try to incorporate all available knowledge about the individual level we end up, with absolute certainty, with an intractable problem (that is, one for which we cannot distil any interesting information out of the differential equation). So we have to compromise and already in the modelling phase we have to keep in mind that the resulting equation should be amenable to analysis. An obvious idea presents itself: use just one variable to describe the state of individual cells and preferably one which can, at least in principle, be measured. This variable should be a reliable indicator of a much more complicated "true" state which takes account of the detailed physico-chemical composition of the cell. As a mathematical idealization we *declare* it to be the true state, that is, we pretend that all relevant information is contained in this one and only variable. The example above concerning the cell size distribution is based on such considerations.

There exists yet another way out of the problem that realistic models tend to be so complex that they become resistant to mathematical analysis (and, in addition, so parameter rich that an experimentalist has to provide a prohibitive number of estimates). When the initial modelling stage is over we may simplify the model through limiting procedures based on i.a. time scale arguments. It is, in general, safer to first formulate a complicated model and only thereafter take limits then to construct the "limiting" models directly (see, for an example, DIEKMANN, NISBET, GURNEY & VAN DEN BOSCH, to appear).

The aim of structured population models is to derive information about the dynamics of populations from information about the dynamics of individuals or vice versa. For instance, in human demography one wants to predict the population growth on the basis of age specific fertility and mortality statistics obtained from civil registration data. In cell kinetics, on the other hand, the experimental inaccessibility of the individual level creates *inverse* problems (e.g. to infer properties of the cell growth rate g and the fission rate b from data about the population growth rate and the stable size distribution, see PAINTER & MARR (1968), BELL & ANDERSON (1967), TYSON & DIEKMANN (to appear), VOORN (1983)).

To further illustrate the applicability of the "structured" approach, I briefly describe two classes of models by listing the i-state variables and the "change" and "creation/destruction" processes, while referring to papers in METZ & DIEKMANN (to appear) for the detailed modelling of these processes.

KOOIJMAN (to appear) describes a *Daphnia* population on the basis of an energy budget. The i-state variables are size, age and storage, the "change" processes ingestion, maintenance, growth and storage and the "creation/destruction" processes reproduction (parthenogenetic) and death (due to aging, predation and possibly starvation). In other words, he derives a detailed model for the relation between food input and neonate output which may be used as a basis for population dynamics. The motivation stems from toxicity research. Toxicity tests are usually done under "abundant food" conditions and it is a priori unclear how the results can be extrapolated to "natural" conditions, depending on the particular physiological process being affected by the toxic chemical. In the context of the model one can actually perform the extrapolation (see KOOIJMAN & METZ (1984) for such a study with a simpler model without storage; also see DIEKMANN, METZ, KOOIJMAN and HEIJMANS, 1984; recently H.R. Thieme has made a profound mathematical study of the Kooijman- Metz model).

SABELIS & LAANE (to appear) describe plant-herbivore-predator systems by characterizing individual patches (one plant or a collection of nearby plants) in terms of the amount of foliage, the number of herbivores in the patch and the number of predatory insects in the patch. The "change"

processes are foliage growth, the eating of foliage and the subsequent conversion into new herbivores, the eating of herbivores by predatory insects and the subsequent conversion into new predators. The "creation/destruction" processes are the formation of herbivore colonies and the invasion of a predator into a herbivore colony. The basic question is: what is the relationship between *local* dynamics (in one patch) and *global* dynamics (in a large collection of plants). The motivation stems from biological control. EDELSTEIN (to appear) discusses similar models for plant-herbivore interaction.

3. WHAT IS THE APPROPRIATE P-STATE SPACE ?

The introduction of Sobolev spaces has made the theory of (elliptic and) parabolic partial differential equations much more elegant and powerful. So the choice of a state space is not without importance.

The convential choice for the p-state space is $L_1(\Omega)$. The standard motivation is that integrals yield numbers. The following two observations suggest that this space is too small:

(i) In age-dependent models all individuals are born with age zero. In the L_1-context we can account for the neonate source term by a boundary condition, but when dealing with the variation-of-constants formula (to verify the principle of linearized stability or to study Hopf bifurcation) this creates all kinds of technical problems (see WEBB (1985a), PRÜ'SS (1983); Schappacher (pers. comm.)). If, on the other hand, we consider the neonate source term as a measure concentrated at age zero (and identify L_1 with absolutely continuous measures) these technical problems disappear as snow in a hot sun (CLÉMENT, DIEKMANN, GYLLENBERG, HEIJMANS & THIEME, in preparation).

(ii) Let the i-state be given by age and size and assume that individuals are born with a fixed size (e.g. the asymmetric cell fission model with age as another i-state variable).
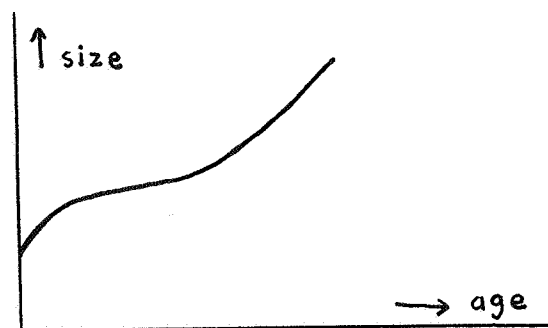
Then the distribution of individuals will concentrate on a line in the age-size plane. Whenever this line is fixed (i.e., whenever the food supply is constant) we can eliminate one variable (say size), but in general this is impossible. So we have to face the situation that with multi-dimensional i-state spaces the i-state distribution may be concentrated on lower dimensional manifolds.

Thus we are led to choose as our p-state space $M(\Omega)$, the space of regular Borel measures, in accordance with the probabilistic interpretation (FELLER, 1966) and the standard motivation that integrals yield numbers. Being the dual space of the space of continuous functions on Ω, M has two natural topologies (the norm or total variation topology and the weak * topology) which both seem to play a role. In the case of a one-dimensional i-state space Ω, the absolutely continuous measures will usually constitute an *invariant* subspace, which brings us back to the L_1-setting. However, observation (i) above shows that even then it may be advantageous to consider explicitly the embedding into the larger space M, while observation (ii) shows that in general this subspace need not be invariant.

4. LINEAR ANALYSIS 1: INTEGRATION-ALONG-CHARACTERISTICS, DUAL SEMIGROUPS AND THE VARIATION-OF-CONSTANTS FORMULA.

Structured population models lead to first order partial functional differential equations. The adjective "functional" is used to express that, as a rule, the source terms contain non-local arguments (e.g. $x + x_0$ in the cell fission equation). The occurrence of these terms complicates the construction of a solution , even in the linear case. A successful strategy to overcome this difficulty is the following. First we simply neglect the source terms (i.e., we put them equal to zero). The resulting easy problem can be solved explicitly by integration along characteristics. When working with measures this is done indirectly: one first solves the pre-dual or backward problem (FELLER, 1966) (which is obtained by replacing the divergence (velocity n) term by -velocity . gradient n and changing the boundary condition appropriately) on the space of continuous functions and subsequently defines the forward solution operator by duality; see HEIJMANS (1984) for an example . Thus we obtain dual semigroups.

Next we add the source terms back in as a perturbation of the generator, replace the full differential equation by a variation-of-constants equation and solve the latter by successive approximations (CLÉMENT et al, in preparation). Biologically this amounts to the generation expansion! This program is not yet carried out in detail for cases in which the i-state space has dimension greater than one.

Linear semigroup theory is very useful since there is a known relationship between computable spectral properties of the generator and the large time behaviour of the semigroup (e.g. WEBB, 1985a, GREINER, 1984).

5. LINEAR ANALYSIS 2: POSITIVITY AND STABLE DISTRIBUTIONS.

Semigroups generated by population equations leave the cone of positive measures invariant. The structure of the spectrum of the generator of a *positive* semigroup is very special (GREINER, 1981, 1984) and consequently so is its large time behaviour. It appears that for linear problems the combination of positivity and irreducibility yields, as a rule, *stable distributions*. The following references contain some more information on this topic: GREINER (1981, 1984), HEIJMANS (1985, to appear) and WEBB (1985 a,b). Sometimes one can actually compute the stable distribution explicitly and use this computation to analyse the inverse problem (TYSON & DIEKMANN, to appear).

6. NONLINEAR AND NUMERICAL ANALYSIS: INTERACTION THROUGH THE ENVIRONMENT.

Frequently the linear structured models contain parameters, such as the concentration of an essential nutrient S, which will only in carefully controlled laboratory experiments be constant. Under more general conditions one has to supplement the equation for n with a dynamical equation for S such as

$$\frac{dS}{dt} = F(S, L[n])$$

where L is the consumption functional. In other words: we close an input -output loop and obtain a nonlinear feedback system. Our aim is to develop a local stability and bifurcation theory for such systems, by using dual evolutionary systems to describe the open input -output circuit, in combination with fixed point arguments.

In addition we want to develop efficient numerical methods for the study of such systems.

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