System Dynamics applied to epidemics

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Abstract

This paper presents an approach to infectious disease analysis through System Dynamics methodology, following the early works of Ritchie-Dunham. The case study concerns the Bovine Leukosis Virus (BLV), that exclusively strikes cattle. The infected animals, exposed to secondary infections, become less productive bringing about an economic loss. In order to avoid the spread of the infection among dairy farms an eradication national plan is operative in Italy since 1996, but points of infection are still being recorded. Hence deeper analyses are required to understand the causes of the endemic behavior of BLV. Analytical models of epidemic spread have been implemented since the first decades of the XXth century, but, their practical use is often difficult. System Dynamics models allow epidemiologists to do a set of what-if analyses, with the purpose of assessing the system's behavior under various conditions, and afterwards, to compare and evaluate the results of alternative sanitary policies.

Keywords: epidemics, health care, public policies, complex nonlinear dynamic systems.

Introduction

Recently two episodes, concerning epidemics on animal farms, have particularly struck the European public opinion: the mad cow and foot and mouth disease. The first one mainly for the tragic consequences that it has had on man. Even if humans are not directly in danger, since the infective agent is not considered able to "jump species", economic damage is however considerable, represented by loss of animals, the negative effects on meat markets, by resources required to control and eradication policies.

Another animal disease with epidemic characteristics is Enzootic Bovine Leukosis, it concerns a viral pathology, sustained by a retrovirus similar to the human retrovirus of HIV, that exclusively strikes cattle. The Leukosis is not deadly for most infected animals, but a small percentage of them develop a malignant form. The infected animals remain serum positives for life, so they are exposed to secondary infections, due to the weakening character of the illness, and consequently become less productive bringing about an economic loss.

In order to avoid the spread of the infection among dairy farms an eradication national plan is operative in Italy since 1996, in accordance with Directive 64/432/EEC on health problems affecting intra-Community trade in bovine animals and swine, and the following Council Directive 97/12/EC.

Notwithstanding the adoption of this plan, with the obligatory elimination of infected animals, cases of endemic character are still being recorded, especially in dairy farms situated in Central and Southern Italy. Figures 1 and 2 report the relative percentages of farms and cows detected as positive in Italy in 1998[1]. Deeper analyses are then required to understand the causes of the endemic behavior of the Enzootic Bovine Leukosis, possibly using new approaches.

As already outlined, the main target of sanitary controls is the total eradication of the disease. To improve the analysis of infection dynamics, with the aim of select the policies with maximum probability of eradication (in the deterministic model of the single farm this target can be translated into "minimum time of eradication") and minimum number of controls, we have built some models of Bovine Leukosis contagion on a typical dairy farm.

Analytical models of epidemic spread have been implemented since the first decades of the XXth century, but, their practical use is often difficult, above all for predictive and quantitative analysis.

A new possible approach is computer simulation, in particular the “System Dynamics” technique, to solve the problem under exam. This article analyzes the potentialities of "System Dynamics" simulation technique applied to the epidemiological field. Developing our models of epidemic simulation we have three goals in mind:

a) to allow the identification of factors and mechanisms of epidemic spread during the descriptive phase;

b) to allow the sifting of different scenarios in a reasonably rapid way;

c) to allow a qualitative and quantitative evaluation of defense strategy choices;

to implement a valid tool in decisional and control processes for those responsible for public health.

In this article we will describe the model of simulation that have been developed and we will also underline the differences between this new approach and the more traditional ones in the mathematical treatment of infectious diseases.

[1] This is the more recent publication from Italian Sanitary Authority available from World Wide Web:
(http://www.sanita.it/alimvet/veterinaria/piani/eradicazione98/leucobov1.html)

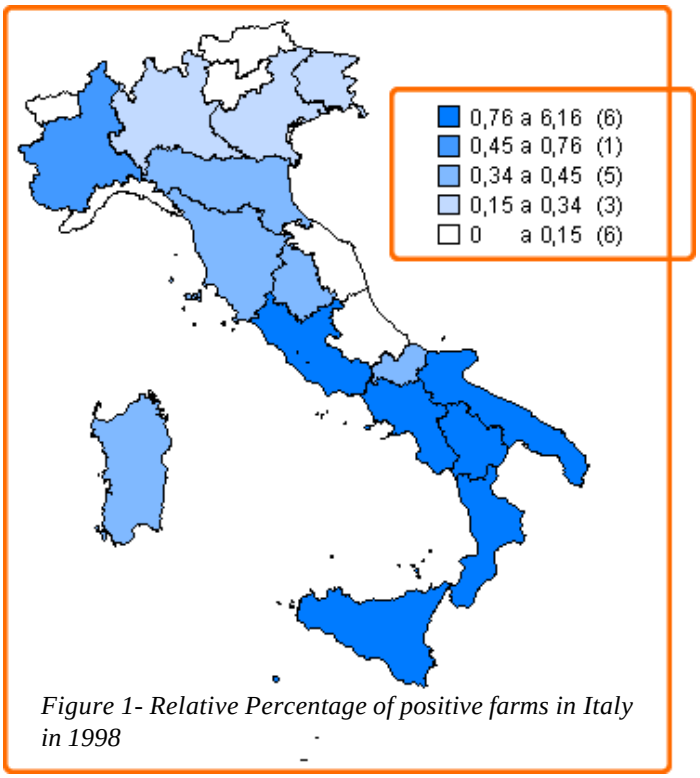


Figure 1- Relative Percentage of positive farms in Italy in 1998

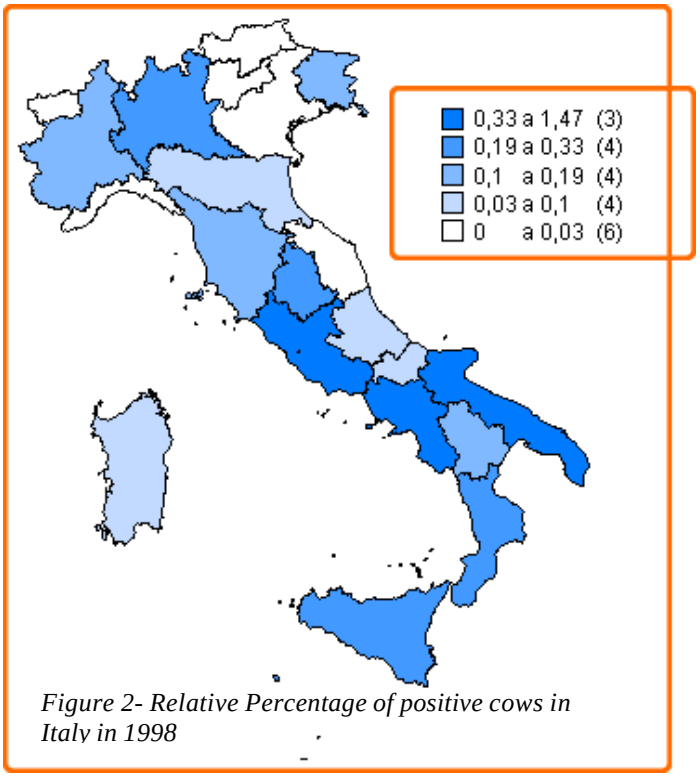


Figure 2- Relative Percentage of positive cows in Italy in 1998

The mathematical bases of the model

The outstanding impact on public health have given impulse to the development of representative models of epidemic evolution and propagation (Bailey 1975) (Bartlett 1960) (Hoppensteadt 1975). The most important, from a historical point of view, and for the number of applications and developed analyses, is the deterministic model (the so-called SIR model), that depicts the spread of infection in terms of time dependent differential equation systems.

Deterministic model SIR

The SIR model (Kermack and McKendrick 1927) (Kendall 1956) is the point of reference for mathematical models used to describe epidemic diffusion. We illustrate here this model, whose differential time dependent equations form the bases of our simulation models.

The model divides population, into three fundamental blocks:

- ✓ s (susceptible) that is subjects susceptible to contract the infection;
- ✓ i (infected) the subjects that have already contracted the infection, to the stage of full development or incubation, so they are vectors of contagion;
- ✓ r (retired) subjects that have died or that have developed immunity to the contagion, therefore no longer able to infect or to contract infection.

Three differential equations describe time evolution of population P components. We suppose P constant to simplify.

$$\begin{cases} \dot{s} = -is\beta \\ \dot{i} = is\beta - i\gamma \\ \dot{r} = i\gamma \\ p = r + s + i = const \end{cases}.$$

Where the meanings of parameters are:

β (infection-rate or contact-rate) rate of new infected in the unit of time;

γ (removal-rate) rate of mortality or immunity in the unit of time.

Therefore we are able to foresee the temporal trend of infection estimating β and γ parameters, and knowing the initial values (s_0, i_0, 0) at time t_0. In practice we are more interested in the derivative of *r*, that is the "epidemic curve", given by the new retired rate. The importance of this curve is due to the format normally available for epidemiological data: the number of new deceased / recoveries in the last unit of time (generally day or week).

The famous Kermack and McKendrick's "Threshold Theorem" has derived from these equations: naming $\rho = \gamma/\beta$ the relative removal-rate, no epidemic can spread unless we

had the initial condition $x_0 > \rho$. Defining $\nu = s_0 - \rho$ and under some approximations, the "total size of epidemic", that is the total number of subjects infected, for $t \to \infty$ is 2ν. In other words:

$$\begin{cases} x_0 = \rho + \nu \\ x_\infty = \rho - \nu \end{cases}$$

In the case of non deadly or non symptomatic disease it is possible to use a simplified model: the SI. It does not keep track of retired ones and solutions are more simple and immediate.

Over the years, the model presented has been extended, by the same authors and by other researchers, to consider other arguments such as: the presence of carriers (apparently healthy individuals who harbour infection), the spread of illnesses through vectors (bugs, water, food, etc.), several groups of subjects coexisting (with different rates of infectivity, mortality and immunity), other states apart from infected / susceptible (for example, immunity from a previous exposure to contagion), the contemporary action of more viral agents, incubation periods and so on.

Despite great results reached in the qualitative and quantitative description of the evolution of infectious diseases, a deterministic model has intrinsic limits, in detail it is not valid:

- ✓ for small populations, in which events are subject to ample statistic fluctuations;
- ✓ for non homogeneous populations with different degree of immunity, density, exposure to contagion factors, etc.;

so its practical use is often difficult, above all for predictive and quantitative analysis.

Other models

Likewise its deterministic counterpart, the **epidemic stochastic model** can be described using random variables $s(t)$, $i(t)$ and $r(t)$, that represent respectively the number of susceptible, infected and retired subjects at time t (with $s(t) + i(t) + r(t) = n + a$ with a initial infected). In an analogy with the deterministic model we define infection and removal rates. We define also a time dependent differential-difference equation system, to determine the probability $p_{si}(t)$ that at time t there are exactly s susceptibles still uninfected and i infectives in circulation.

However, as in the case of the deterministic model, the main problem is to apply formulas to real world.

Other models have been developed that keep track of the geographical distribution of population components (S,I,R), besides the temporal one: these are **"spatial models"**. In other terms the above differential equations describing the spread of infectious disease are not only dependent on time but also on two-dimensional coordinates (x, y). So that we analyze the gradients of the functions $s(x, y, t)$, $i(x, y, t)$, $r(x, y, t)$.

Another important class of models no longer consider processes that occur in continuous time but assume that, following the contraction of infection by any susceptibles, there ensues a latent period of fixed length. The subsequent infectious period is considered as being contracted to a single point of time. These are the so called **discrete-time** or **chain-binomial** models (Gani 1969) (Gani and Jerwood 1971).

If we also suppose that a susceptible chance of being infected depends only on the presence of some infectives and not on their actual number, we obtain the Greenwood model.

If we assume instead, that the chance of infection does depend on the number of infectives present we obtain the Reed-Frost version.

Because the focus of this paper is the use of simulation models, it's important to remark that **Monte Carlo techniques** have been already used (Elveback et al. 1971) (Elveback 1971) (Ewi et al. 1972) (Gallop 1999) to challenge the complexity of stochastic models and Markov chain models.

The case study

Enzootic Bovine Leukosis is a viral pathology (BLV) sustained by a retrovirus from the same family as HIV that exclusively strikes cattle. BLV is not fatal for most infected animals, although they remain serum-positives for life. Hence, due to the weakening character of the illness, they are exposed to secondary infections, and consequently become less productive. Moreover, serum-positive cattle are ineligible for selling.

In order to avoid a great increase in the spread of the infection among farms and to improve the efficacy of legislation prohibiting the sale of infected animals, rapid identification and elimination is essential. Therefore, since 1996, an obligatory national plan for eradication following sanitary controls at frequent intervals has been set up in Italy. The frequency of the controls depends on the identification of cases of infection. The adoption of this plan has certainly contributed towards the limitation of the spread of the infection, but, to date, cases of endemic character are still being recorded, especially in dairy farms situated in Central and Southern Italy.

This study was developed jointly with 'Istituto Zooprofilattico Sperimentale delle Regioni Lazio e Toscana'. The epidemiologists' aims onto investigate the causes of endemic behavior of BLV in some farms of Central Italy, and to appraise the effectiveness of various control measures as alternatives to current ones.

Epidemiological issues

Bovine Leukosis is a weakening disease which occurs over a long period of time. Along this period the chances of eliminating an infected bovine (retirement or death) from the farm due to appearance of symptoms are practically negligible; so that the mathematical reference model do not consider the "retired" in a classical way. Moreover, an infected animal cannot regain its health, neither can it develop a kind of immunity. Hence animals that are detected as infected at periodical controls are butchered.

Other aspects of epidemiological interest are the period of latency, of about two weeks, during which the animal is already infected but cannot transmit the disease to other

animals, and a period of serum-conversion, of about 17 days, in which the infected (and infectious) animal is not detectable at tests. Therefore, for the simulation of the control activities, it is necessary to distinguish between infected animals that are detectable and those that are not.

The situation is even more complex for young calves, in which the simultaneous action of infective factors (blood and colostrum) and antibodies eventually assumed through milk, can increase the resistance to the disease for a period of around six months. All this can be represented in the model with a degree of immunization[2] which is diversified between adults and young bovines, although at an initial stage of simulation we assume a single degree of immunity in order to simplify the model.

Other important epidemiological subjects are different ways of transmission of the disease. Basically the means of transmission represented in the model are:

- ✓ direct contact between animals of the same department;
- ✓ simultaneously gynaecological visits in homogeneous groups of animals of the same sector of the farm;
- ✓ transplacental transmission at the moment of parturition;
- ✓ administration of milk of an infected bovine to young calves in their first days of life;
- ✓ injections carried out for the administration of vaccines.

From the evidence reported by experts it is clear that the course of an epidemic of BLV depends on the interaction between the cows and the logistic aspects of the farm.

The operative ways dairy cows are managed on the farms are strictly related to their physical conditions, in particular to their ability to yield milk and to their possible pregnant state. These aspects reflect the organisation of the dairy farm that is structured in several sectors which are physically separated, each containing a homogeneous group of animals.

In our simulation models, we have considered a typical medium - large farm from the centre of Italy with a population of a few thousand cows and seven physical sectors which bovines pass through depending on specific events like birth, growth, pregnancy, delivery, nursing, etc. During their lives, usually about five and a half years, the cows go into calf areas immediately after their birth and subsequently they complete the production cycle (insemination, pregnancy, delivery and nursing) three times on average.

The controls

The Italian control policy for bovine Leukosis consists, at the moment, of periodic tests conducted on the animals by the Veterinary Services, in correspondence with the national plan for eradication of the disease. Such controls are limited to the cows of ages older than twelve months.

[2] that is the resistance to also contract the infection following exposure to infective factors.

The dairy farms that do not exhibit cases of Leukosis acquire a sanitary warranty, in order to be able to sell animals. On the other hand, the presence of infected animals determines the carrying out of controls at closer intervals. The farms get the sanitary certification again after two negative consecutive controls, the second of which is performed after a period of quarantine.

In the case of positive controls the farm must eliminate all the infected cows within one month. According to empirical evidence and to simplify the structure of the simulation, we assumed that all the infected animals are butchered at the end of the period allowed for this operation and hence the latter test is carried out two months after the former.

Simulation

As an alternative to methods used so far to define epidemic descriptive / predictive models, we have developed a new approach through computer simulation, using "System Dynamics" paradigms (Forrester 1961).

Building an epidemic model using System Dynamics archetype, as in Hemorrhaging Dengue Fever study (Ritchie-Dunham 1995a) (Ritchie-Dunham 1995b), we focus on time dependent differential equations systems and their iterative solutions. The population characteristics are aggregate variables and the model describes the change of these variables as a whole system.

The main sources of information were interviews with the subject-matter experts, evidence taken from scientific literature concerning estimates of the infectivity ratios of the various ways of transmission and a first series of real data acquired from a medium-large Italian dairy farm.

We used the commercial product "Vensim" to implement our models.

Some details of model

Here we resume and list the fundamental characteristics of the deterministic model, whose picture we can see in Figure 3.

- ✓ We have three stock variables: susceptible, infected and detectable subjects, and transitions between the three stocks are adjusted according to the SI contagion model basis idea.
- ✓ Only susceptibles and detectables are measurable variables. The infected is a variable that is fundamental, influences other variables and obviously affects the model behavior. However, the observer will never know its value as already stated in the discussion on serum-conversion period in "Epidemiological issues".
- ✓ The life cycle of dairy cows passes through seven physical sectors and nine logic states. The mean times of permanence in the various sectors are determined by physical characteristics of cows (lifetime, gestation time and so on).
- ✓ The overall number of cows tends to be stable in the neighborhood of the firm's target. This is because we are examining a farm whose production is milk so that the company would like to manage cows as far as possible at the upper bound limit

established by logistic considerations. Retired animals are replaced as soon as possible, any surplus in numbers is drained by selling calves in excess, all the males born on the farm are sold within about eleven days of birth.

The sanitary controls are scheduled on an annual basis if the farm has the sanitary warranty. If an infected animal is detected, the farm will lose the sanitary warranty and, at the same time, controls will be scheduled at closer intervals until two consecutive controls, the second performed after a period of quarantine, give negative results.

All dairy cows detected during scheduled controls are butchered in a single day, the unit time of our model, so that the retired is a pulse function, whose schedule depends on actual sanitary warranty and the previous number of detectable subjects, and whose amplitude depends on the previous number of detectable subjects.

Researchers can set up simulated sanitary controls to build different scenarios (see Fig. 4), varying: the initial control time, the delay between two controls when the farm has the sanitary warranty, the delay between two controls when the farm is in quarantine and the delay after the quarantine. There is also a "control type" variable to set: no controls, controls on animals older than twelve months, controls on all animals.

The stock array variables have nine rows: Cages, Growth, Calves, pregnant Calves, Dries, Delivery room, Feeding, Production, pregnant Cows. These are a mix between physical sectors of farm, and logical conditions of Cows; anyway they are fundamental factors for epidemic spread.

They are connected by feedback to the flows of the newly infected that depend on intra-sector infection rates (contact and iatrogenic) and on the infected subjects within the same sectors, in the same way as they depend on inter-sector (contact and colostrum) infection rates and on infected subjects from other sectors. Of course, flows and feedback are of array type too.

There is also another continuous flow for the same stock (an auto loop) from one sector to the subsequent one, its size depends on stock size and from the inverse of its mean time of permanence.

The stability of the total number of cows on the farm, is guaranteed by making a comparison with the desired farm target that is also the initial population. Differences are balanced by an input flow to represent animals bought or sold, this way retired animals are replaced as soon as possible.

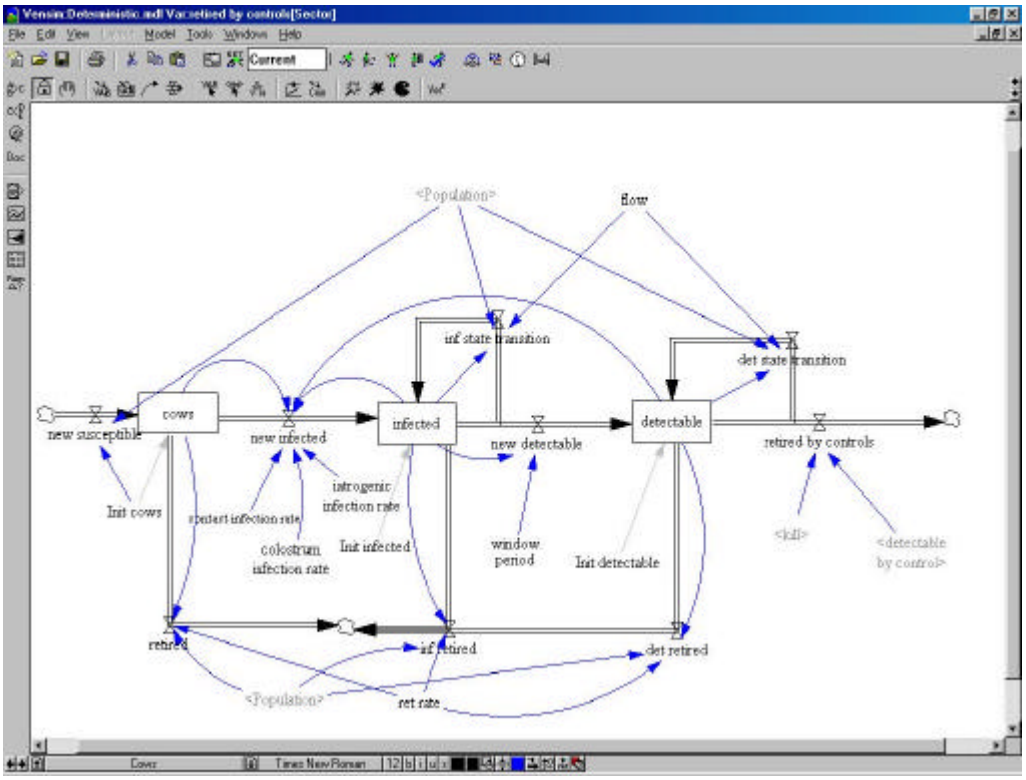


Fig. 3 - the sketch of the model

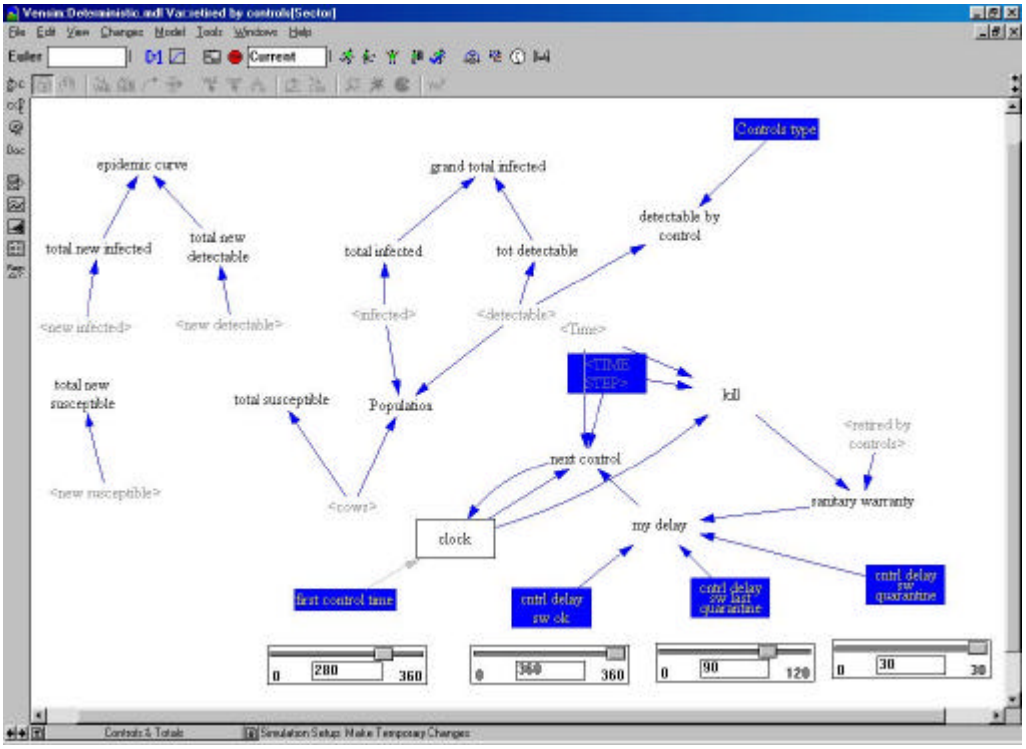


Fig. 4 - the sanitary controls

The model produces two types of output. The first one is a “control output”, to verify the correctness of model. It sketches for the simulated dairy farm:

a) the number of susceptible cows, for each sector;

b) the number of infected cows, for each sector;

c) the number of detectable cows, for each sector;

d) the total sum of infected cows and of detectable, the sum of cows that are able to transmit the disease.

The second one is an output to depict the dynamic of the system, not only in terms of time development but in terms of stability too. So we have:

e) the classical epidemic curve, i.e. the total sum of new infected, detectable, infectious, for each time step (a very important curve in epidemic analyses), in other words the derivatives;

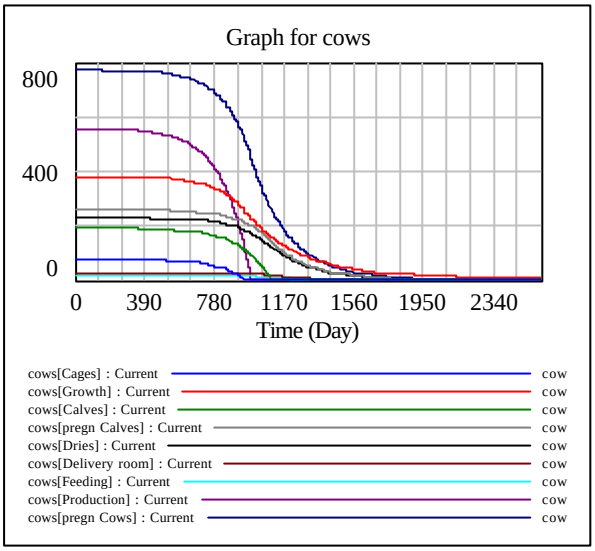
f) the epidemic orbit projections (two graphs): these are the projections on two-dimensional surfaces of the infection represented as a point in multidimensional phase space, in other words it is a snapshot of the dynamic behaviour of the whole system so that the stability or instability of the system may be seen at a glance;

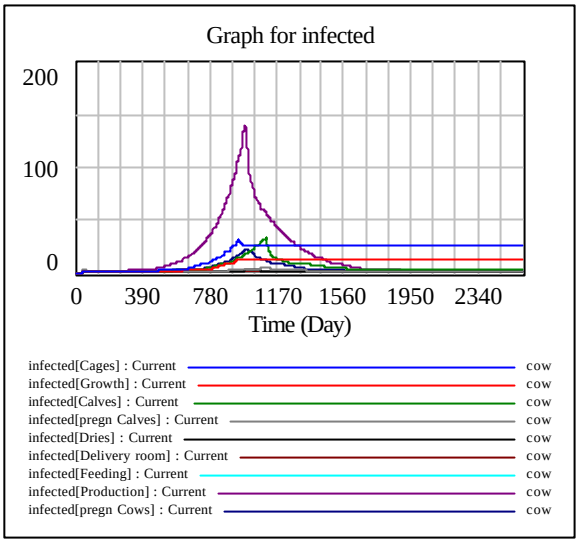
g) the number of retired subjects due to scheduled controls.

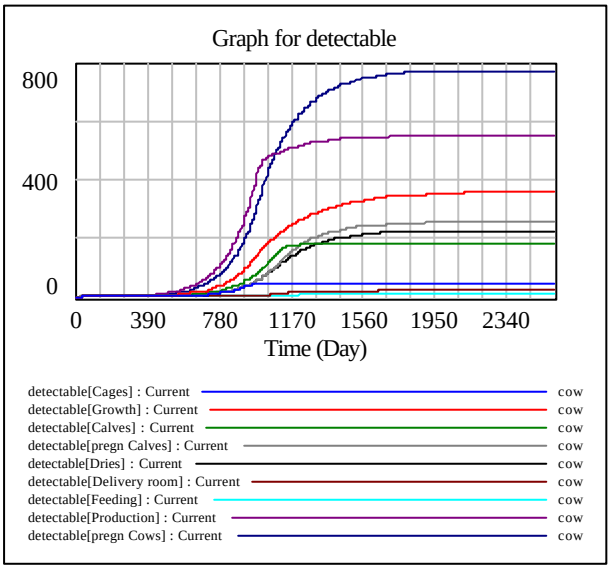
We show, as an example, the results of two runs:

- ✓ in figures 5 and 6 we can see the epidemic evolution when we have an external shock of 4 infected animals in "pregnant calves" sector at day 30, and no controls
- ✓ in figures 7 and 8 we can see the epidemic evolution for the same shock but actual veterinary controls are applied.

We have designed a first stochastic counterpart of this model too, applying the Poisson distribution to flows with deterministic estimation as expected value. The stochastic model is actually under development and evaluation.







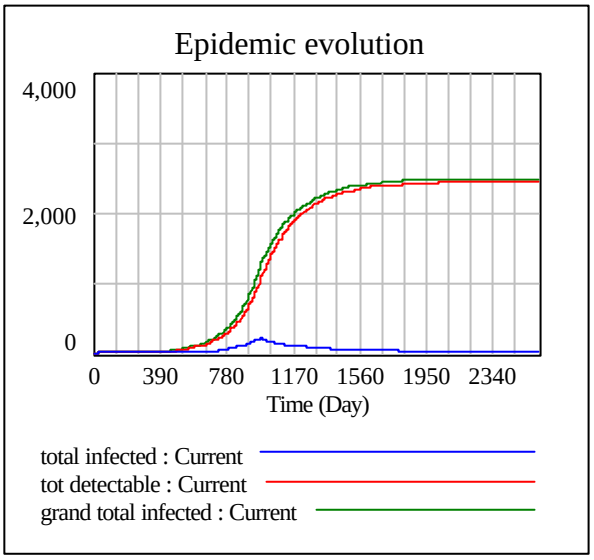


Fig. 5 - first group of graphs, 4 infected at time 30, without controls

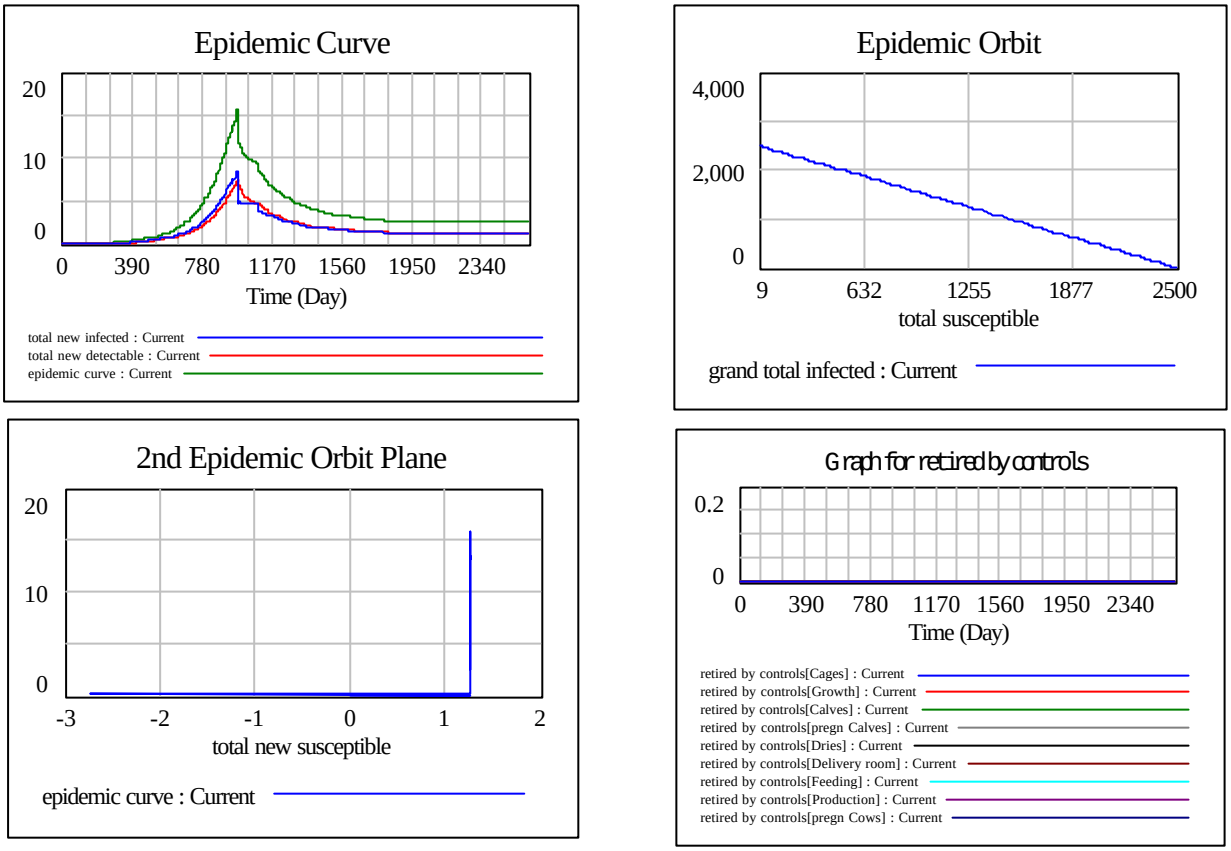
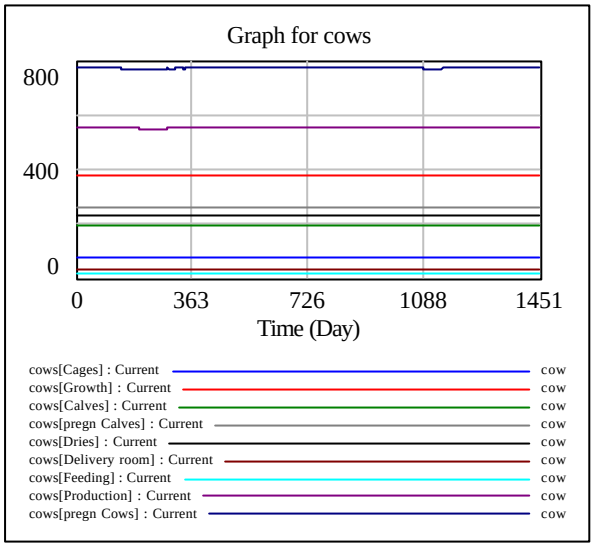
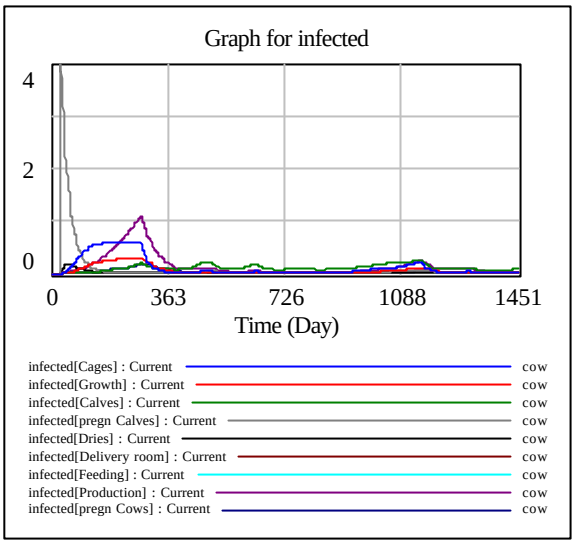
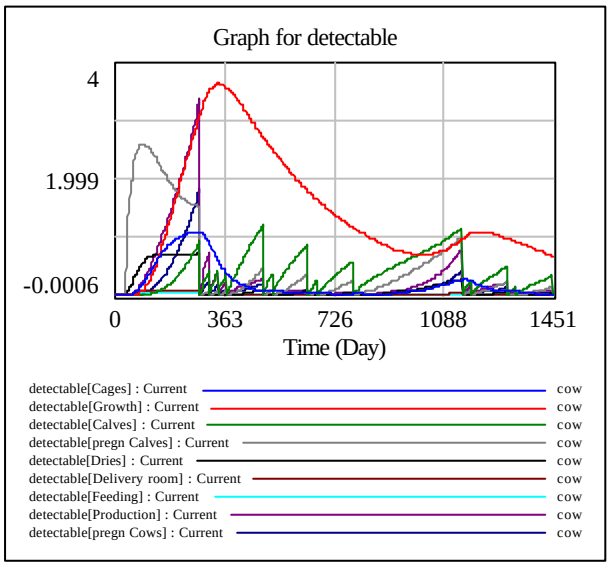


Fig. 6 - second group of graphs, 4 infected at time 30, without controls







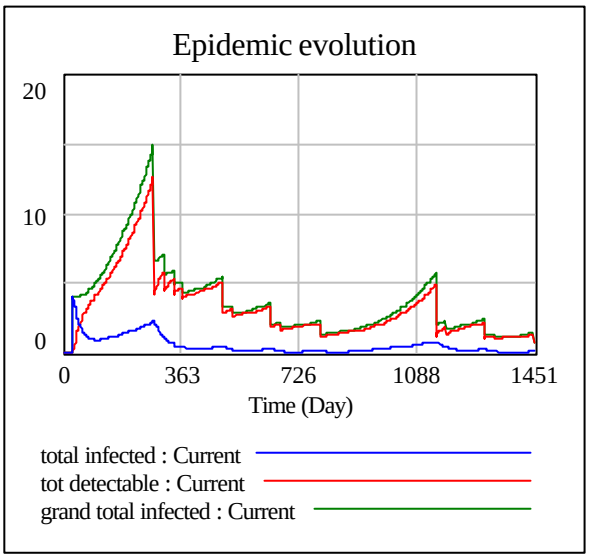


Fig. 7 - first group of graphs, 4 infected at time 30, with "standard" controls

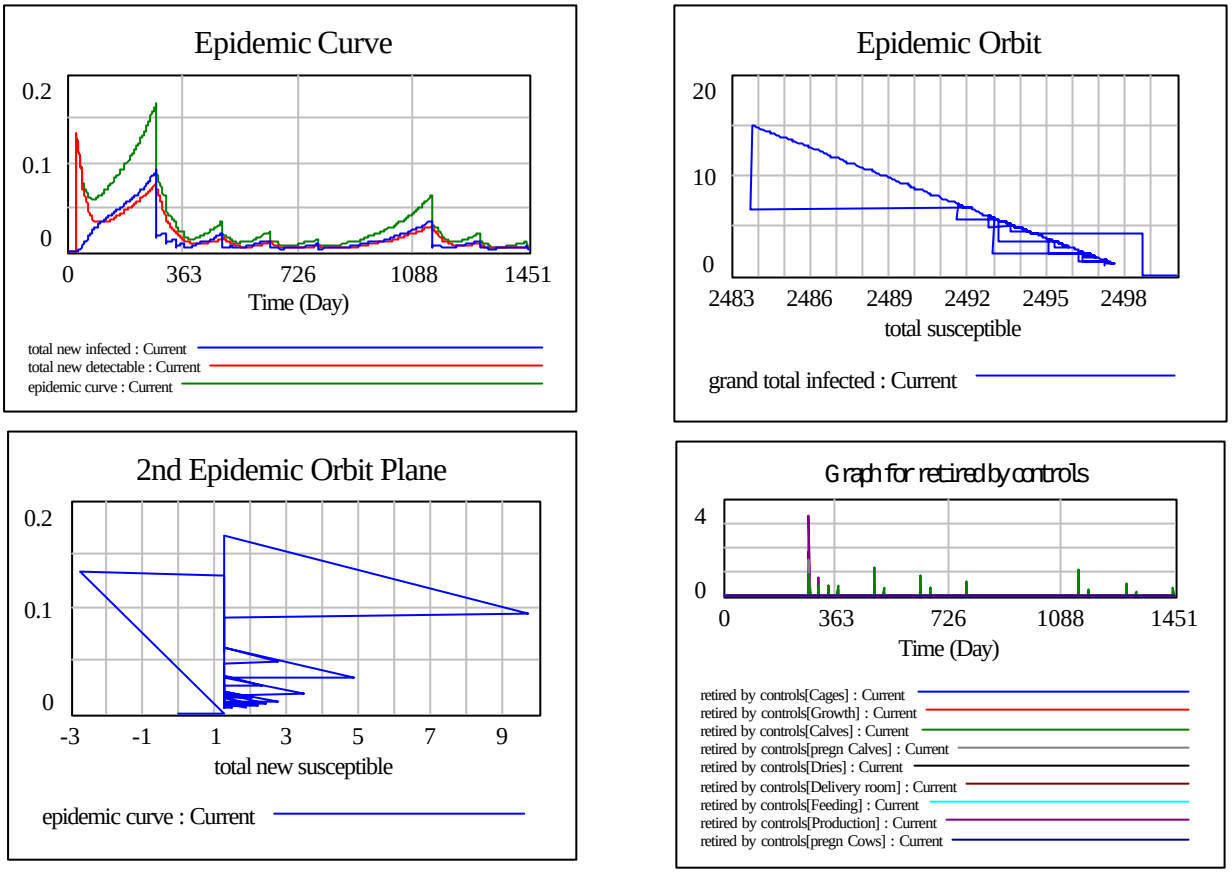


Fig. 8 - second group of graphs, 4 infected at time 30, with "standard" controls

Conclusions

First results

The constructed model allows the user to regularly monitor the simulation by means of a series of graphs, as well as to customize experiments by changing characteristic quantities of the system at the initialization step.

The most evident improvement in the use of the simulation is the availability of conspicuous quantities of artificial data, hardly ever obtainable in the real world, because of the elevated costs of polls or the rarity of phenomenon. This has allowed the experts to do a preliminary "what-if" analysis with the purpose of assessing the system's behavior under various conditions and evaluating which alternative policies to adopt.

Thanks to model results, the "Zooprofilattico" Institute researchers have hypothesized that disease may be endemic because of the failure of the current methods of control in the identification of the very young infected calves. These can start a new process of the spread of infection between one control and the following one.

The values of parameters have been inferred by current literature, from the experience of researchers and from some data results picked up from the field.

Using optimization and "goal seeking", offered by the Vensim product, we were able to conduct a first verification of the hypothesized infection rates. A calibration model was developed to match real data collected on field. The first results of parameter values matches very well that available in veterinary literature obtained by experiments.

Other more precise hypotheses, and their validations, will however, only be possible using a model whose parameters are well calibrated. So it becomes necessary to receive more data from the field and extend the model with other necessary elements to fit phenomenon fully.

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