Parasitology

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A mathematical modelling approach for treatment and control of *Echinococcus multilocularis*

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Research Article

Cite this article: Khan A, Ahmed H, Sohail A, Alam F, Simsek S (2020). A mathematical modelling approach for treatment and control of *Echinococcus multilocularis*. *Parasitology* **147**, 376–381. https://doi.org/10.1017/S0031182019001720

Received: 30 July 2019
Revised: 9 November 2019
Accepted: 10 November 2019
First published online: 8 January 2020

Key words:
Control; *Echinococcus multilocularis*; fox; modelling; Petri net

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Abstract

Alveolar echinococcosis (AE) is a zoonotic parasitic diseases caused by a cestode parasite known as *Echinococcus multilocularis*. The parasite has a wildlife cycle with definitive hosts (foxes) and small mammals as intermediate hosts (rodents) while humans are the accidental hosts. Parasite infection pressure relation to time of the year and age dependent infection pressure for parasite abundance also depend on the urbanization. The aim of current work is forecasting the thresholds *via* the computational analysis of the disease spread which is a useful approach since it can help to design the experimental settings with better planning and efficiency. Network analysis when interlinked with the computational techniques provides better insight into the spatial and temporal heterogeneities. In the present study, a mathematical framework that describes the transmission dynamics and control measures of *E. multilocularis* in foxes is documented. We used treatment of foxes with baits for the prevention of the *E. multilocularis* infection. A novel approach of networking, called Petri net (PN), based on density dependent differential equations, is utilized during this research. The accurate description of the transmission of the parasite and the effect of drug on it is provided to the readers in this article. The transitions, which are difficult to analyse theoretically, are presented with the aid of the discrete approach of networking. A discrete mathematical framework can prove to be an accurate and robust tool to analyse and control the parasite dynamics.

Introduction

Pakistan is mainly an agricultural country, having rich natural resources, appropriate climatic conditions, favourable lands and water resources, thus the country has enormous potential for livestock production. Agriculture is playing an important role in the economy of Pakistan by contributing about 21% to gross domestic product, employs 45% of the total work force and 60% of its rural population depends upon this sector for its livelihood (Rehman *et al.*, 2013).

Echinococcus multilocularis is one of the zoonotic tapeworms among the different species of Taeniidae family. It is mostly located in northern hemisphere especially in Asia and Europe. This parasite completes its life cycle in two types of host namely definitive hosts (fox) and intermediate hosts (rodents) while humans are the accidental hosts. It is responsible for causing disease known as alveolar echinococcosis (AE) in a metacestode stage in which small cyst is formed known as locules which spread inside the body through blood and lymph and reach to the internal organs i.e. liver, lungs, kidney and brain (Eckert and Deplazes, 2004).

AE is one of the chronic life-threatening infections, which could have endemic resource-poor settings and high economic impact. The geographic distribution is expanding and this pathogen is considering emerging and re-emerging entity in many countries. The risk of AE increases due to the presence of infective eggs present in food, water, environment and their accessibility to humans (Eckert *et al.*, 2011).

The high prevalence (23.9–57.3%) of *E. multilocularis* among red foxes is reported from Europe. In Europe, *Vulpes vulpes* (red fox) is responsible for AE and harbouring heavily infected animals and this parasite burden is being responsible for the parasitic environmental egg contamination. The parasite distribution is expanded due to the control of successful rabies campaigns. However, it is not exploring until now whether parasite remains undetected or range of *E. multilocularis* has recently extended. Biological behaviour of larval *E. multilocularis* in human is similar to a malignant tumour that is determined by growth of damaging tissues and metastasis to distant organs. The disease has a high mortality rate (more than 90% within 10 years and virtually 100% within 15 years of the onset of symptoms) in untreated cases (Reuter *et al.*, 2001).

The exploratory study of the data showed that foxes up to 3 years' age, represented 86% of total samples, responsible for about 88% of all the infected animals and harboured up to 94% of the total parasite biomass (Fischer *et al.*, 2005). Comparing the transmission models possible changes in infection pressure or acquired immunity were compared to analyse the hypothesis that parasite induced immunity, spatial differences, host age and seasonality may be the

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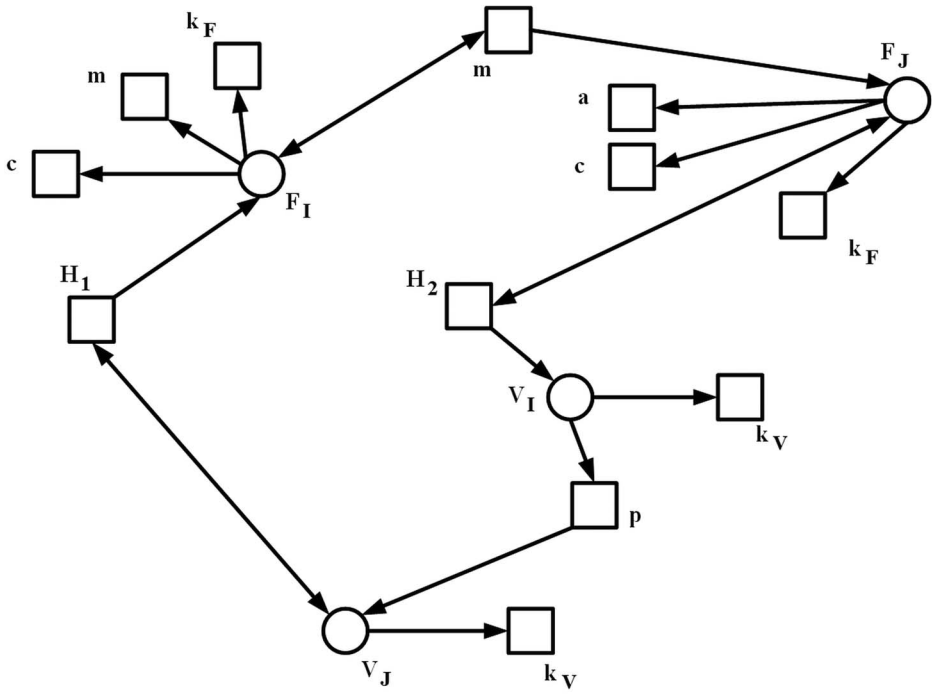


Fig. 1. PN modelling fox & vole interactions.

Table 1. Description of each variable along with transition rates

Symbol	Definition
F_I	Infected fox
$H_1(F_sV_J)$	Hill function
M	Inverse of worm maturity rate in fox
k_F	Death rate of fox
C	Control measure
A	Inverse of adult worm life expectancy in fox
$H_2(F_JV_s)$	Hill function
P	Inverse of maturity of cyst in vole
k_V	Death rate of vole
F_J	Infectious foxes
V_J	Infectious vole
V_I	Infected vole

contributing factor of the abundance parasite in the foxes. Most of the study reported showed a gradual decrease in the prevalence of parasites from rural areas and the periphery of the different cities towards the urbanized zones (Reperant *et al.*, 2007).

Foxes in transition areas of the city and outside areas are more exposed rodents and prey are likely more exposed to parasite infection. The high density of intermediate hosts bearing a high number of parasites and are responsible for prevalence in outskirt of cities. Control of the *E. multilocularis* can be possible through the judicious use of praziquantel baits distributed to foxes (Heglin and Deplazes, 2008) and also represent the *E. multilocularis* abundance in the animal host of different age groups.

However, whatever the intervention strategy, the economic efficiency of control will depend upon the societal burden of disease. In the recent literature, networks, specifically the discrete networks have attracted the attention of researchers enormously due to their association with the biological insight and diversity, such as studies reported by many more (Heiner *et al.*, 2008; Sohail, 2019; Wootton *et al.*, 2019). However, for epidemics and specifically a study focusing on the drug administration through Petri net (PN) modelling approach has not been reported in the literature. We, in this study present for the first time, application of a novel strategy to explore the epidemiology of fox and vole and the *E. multilocularis*, where the control measure is discussed with the aid of Hill function formalism and with the aid of PN modelling (Fig. 1).

Materials and methods

The mathematical model, highlighting the impact of intra and inter fox & vole interactions, initially provided by Roberts & Aubert (Brochier *et al.*, 1991) is utilized as a benchmark in this research. We have used the Hill function formulation, which has been used a successful tool in the field of computational biology to describe the dynamic solver a period, in a more realistic manner (Reperant *et al.*, 2007).

Control measures via mathematical modelling of fox & vole interactions

We have considered the following mathematical framework to elaborate the interactions and the control measures:

$$\frac{dF_I}{dt} = H_1(F_S V_J) - mF_I - k_F F_I - cF_I \quad (1)$$

$$\frac{dF_J}{dt} = mF_I - aF_J - k_F F_J - cF_J \quad (2)$$

$$\frac{dV_I}{dt} = H_2(F_J V_S) - pV_I - k_V V_I \quad (3)$$

$$\frac{dV_J}{dt} = pV_I - k_V V_J \quad (4)$$

In Table 1, $H_1(F_sV_J)$ represents the Hill function which is used in this study to forecast the interaction of infected vole with the

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Table 2. Description of each variable along with transition rates

Symbol	Definition
S	Susceptible fox
T	Age of the host
M	Parasite abundance
γ	parasite death rate
μ	Loss of immunity
A	Rate of acquisition of immunity
H	Infection pressure in number of parasite per year

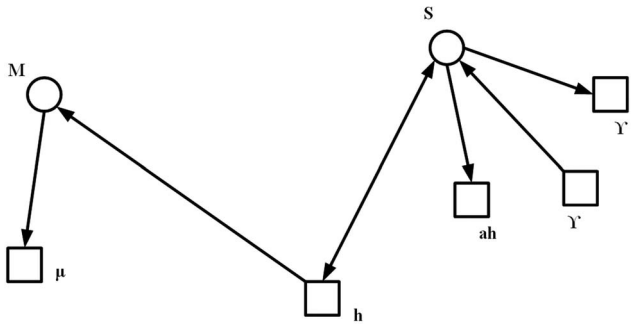


Fig. 2. PN model represents the transmission model for *E. multilocularis* in an animal host.

susceptible fox and $H_2(F_sV_J)$ represents the Hill function which is used in this study to forecast the interaction of susceptible vole with the infected fox. M presents the inverse of the average time to maturity of the worm in the fox and a is the inverse of adult worm life expectancy in fox and p is the inverse of the average maturity of cyst in vole (Table 1). In equation (1) $H_1(F_sV_J)$ represents the Hill function which is used in this study to forecast the interaction of infected vole with the susceptible fox F_s. It becomes infected at the rate of m that actually represents the inverse of the average time to maturity of the worm in the foxes. Next, k_FF_I is the death rate of infected foxes. c is used to present the effect of the control measure against the infection in the foxes. In equation (2) m is the maturity of the worm in the infected fox i.e. F_I. It became infectious at the rate of a, k_FF_J is the death rate of infectious foxes. In equation (3) $H_2(F_sV_J)$ represents the Hill function which is used in this study to forecast the interaction of susceptible vole with the infected fox. And a is the inverse of adult worm life expectancy in fox. Infected vole becomes infectious at the rate of P, and k_V is the death rate of infected vole V_I. In equation (4) infected fox become infectious at the rate of P. k_VV_J is the death rate of the infectious vole. Tables 1 and 2 provide the model parametric values and their respective definitions.

Equation (5) represents the number of susceptible parasites, and is used to represent the rate of loss of immunity in susceptible parasite. a is the rate of acquisition of immunity and h is the infection pressure in parasite. In equation (6) M is the parasite abundance and ah use to represent the infection pressure in susceptible parasites. γ is the death rate of parasite (Table 2).

$$\frac{dS}{dT} = \gamma - (\gamma + ah)S \tag{5}$$

$$\frac{dM}{dt} = hS - \mu M \tag{6}$$

Table 3. Description of each variable along with transition invariants PN fox & vole interactions

Transition invariants	Explanation
$F_J \leftrightarrow H_2 \rightarrow V_I \rightarrow k_V$	Infectious foxes F_J interacts H_2 susceptible vole with infected fox (at rate m 1/(mean time to maturity of warm in foxes)) and then interacts with vole death rate k_V.
$F_J \leftrightarrow H_2 \rightarrow V_I \rightarrow p \rightarrow V_J \rightarrow k_V$	Infectious fox F_J interacts with H_2 infected voles and susceptible foxes (at rate m 1/(mean time to maturity of warm in foxes)) with p as 1/(mean time to maturity rate of cyst in vole) become susceptible vole V_J then the k_V vole death rate.
$F_I \leftrightarrow m \rightarrow F_J \rightarrow k_F$	Active susceptible F_I interacts (at rate m 1/(mean time to maturity of warm in foxes)) and interact with both susceptible or infectious foxes F_J then the fox death rate k_F.
$F_I \leftrightarrow m \rightarrow F_J \rightarrow a$	Active susceptible F_I interacts with m 1/(mean time to maturity of warm in foxes) and m interact both susceptible or infectious foxes F_J and then with a 1/(mean life expectancy of adult worms in foxes).
$V_J \leftrightarrow H_1 \rightarrow F_I \rightarrow c$	Interaction of infected vole V_J with H_1 infected vole susceptible foxes or with infectious fox then interact with the c additional mortality of adult parasites due to control (control effort).
$V_J \leftrightarrow H_1 \rightarrow F_I \rightarrow m$	Interaction of infected vole V_J with H_1 infected vole and susceptible fox then interact with m 1/(mean time to maturity of warm in foxes).
$V_J \leftrightarrow H_1 \rightarrow F_I \rightarrow k_F$	Interaction of infected vole V_J with H_1 infected voles and the susceptible foxes interacts at k_F fox death rate. Active susceptible F_I interaction at rate m
$F_I \leftrightarrow m \rightarrow F_J \rightarrow c$	Interacts with c additional mortality of adult parasites due to control (i.e. control effort).

Table 4. Description of each variable along with the transition invariants PN model of *E. multilocularis* abundance in foxes

Transition invariants	Remarks
$S \leftrightarrow h \rightarrow M \rightarrow \mu$	Susceptible fox S interacts with h infection pressure in parasite and h interacts with the M Parasite abundance at the rate of μ parasite death rate.
$\gamma \rightarrow S \rightarrow \gamma$	Loss of parasite immunity γ interacts with the susceptible host S with γ rate of loss of immunity in parasite.
$\gamma \rightarrow S \rightarrow ah$	Loss of parasite immunity interacts γ with the susceptible host S with an infectious parasite stage at the rate of ah.

PN model to depict the transmission model for *E. multilocularis* in an animal host (fox) is shown in Fig. 2.

Transition invariants

The most important property of PN in biological modelling is the transition invariants (T-invariants) (Tables 3 and 4). Using PN models, our qualitative analysis was focused on identifying two properties (place invariants and transition invariants). Place

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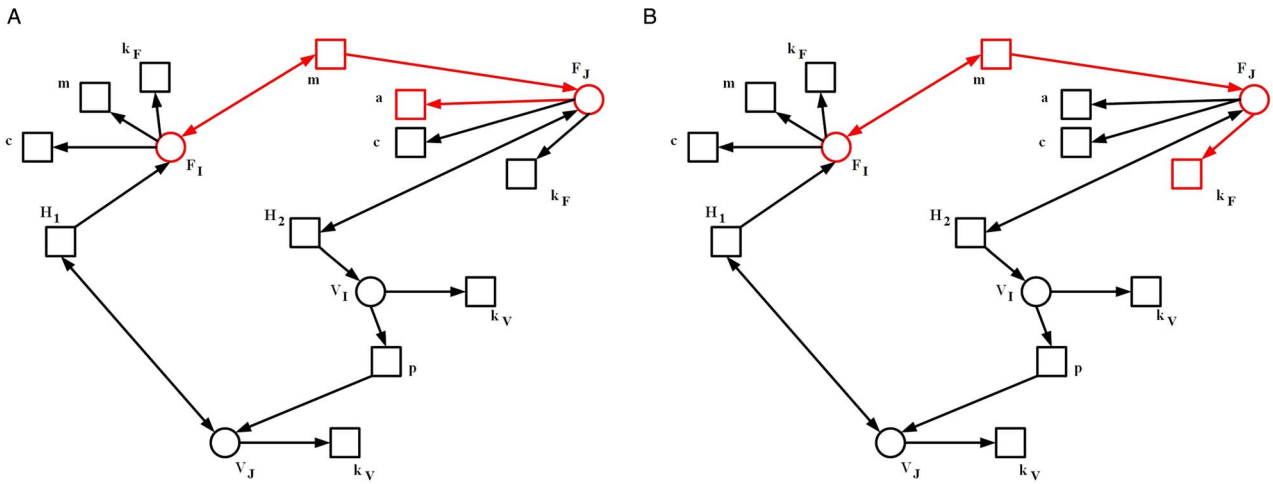


Fig. 3. PN modelling of the fox and vole interaction. Left panel presents the dynamics documented by the first two terms of equation (2). Right panel presents the dynamics documented by first and third terms of equation (2).

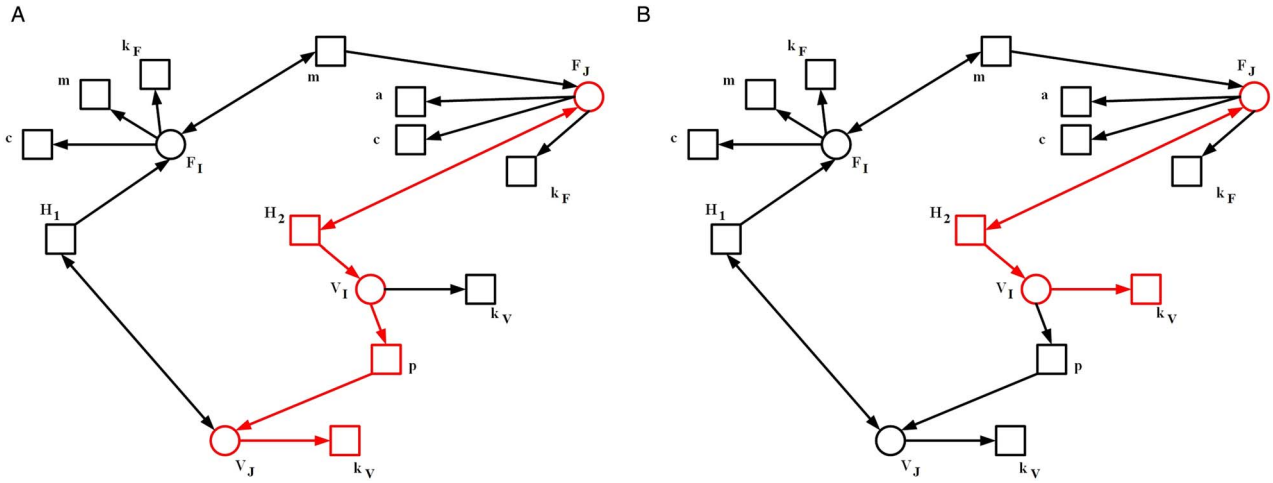


Fig. 4. PN modelling of the fox and vole interaction. Left panel presents the dynamics documented by the first and second terms of equation (3) and first and second terms of equation (4). Right panel presents the dynamics documented by first and third terms of equation (3).

invariants are for characterizing relationships among variables, while transition invariants are for identifying a set of sub-networks in the overall network. In this paper we are using only transition invariant in the quantitative analysis, we obtained the PNs and compared them with the results obtained from Ordinary Differential Equations (ODE's). Transition invariants are a set of transitions where their sequences of firings can be reproduced in the specific states.

During this research, we have derived the transition invariants for both models using technical programming language. We have presented the details of the transitions, which can help in analysing the real transition from one compartment to other in both models. The purpose of this study is to provide a network analysis that can help to forecast such thresholds. In this paper we presented the transition invariants *via* a quantitative approach of PNs. This approach is recommended for future control measurements.

Results and discussion

During this research, we have documented the interplay between the terms involved in the system of differential equations and the networks associated with them. The results obtained after sketching the networks and the corresponding transition invariants are listed below step by step.

Firstly, the left panel of Fig. 3 was discussed. Here, the dynamics associated with mF_I, i.e. the density of infected fox, with the Hill function of infectious fox and susceptible vole was explained. This image presents the major transition invariant of the PN, which were not that clear from equations (1) and (2). Similarly, Figs 2–4 depict the interesting features of the mathematical model in a novel way. These transitions are explained in detail in Table 3. Figures 4–6 presents the dynamics of infected fox & vole and infectious fox &vole with the passage of time, over a period of 50 weeks (nearly a year). The parametric values were selected from Eckert *et al.* (2011) and Fischer *et al.* (2005).

When no control measures were applied, the frequency of cases reported for the infected fox, accumulated after a period of 10 weeks at a higher rate. After introducing fewer control measures (Lucius and Bilger, 1995), this frequency was controlled, and it remained almost equivalent to the number of the infected fox cases reported initially. However, for the higher control measures, the response was quite more than normal.

There is only a published report on *E. multilocularis* from Pakistan. It was reported in human and cattle from KPK province of Pakistan by using Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Out of 30 cattle samples, 13 (43.3%) were found to be positive for *E. multilocularis*. On the other hand, among 10 human samples, 3 (30%) were

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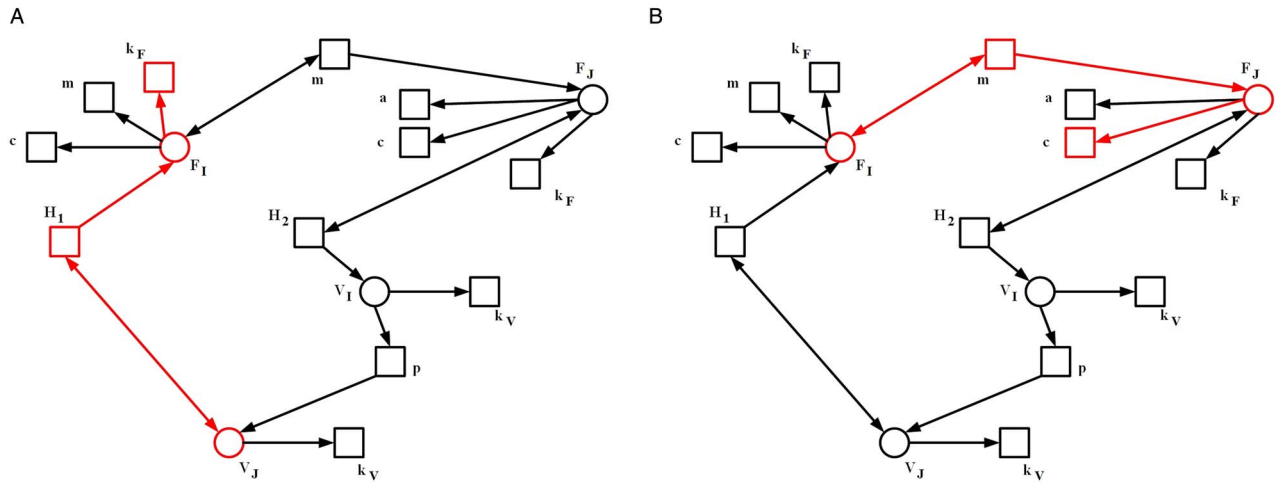


Fig. 5. PN modelling of the fox and vole interaction. Left panel presents the dynamics documented by the first term of equation (1), first and third terms of equation (1). Right panel presents the dynamics documented by the second term of equation (2) and the fourth term of equation (2).

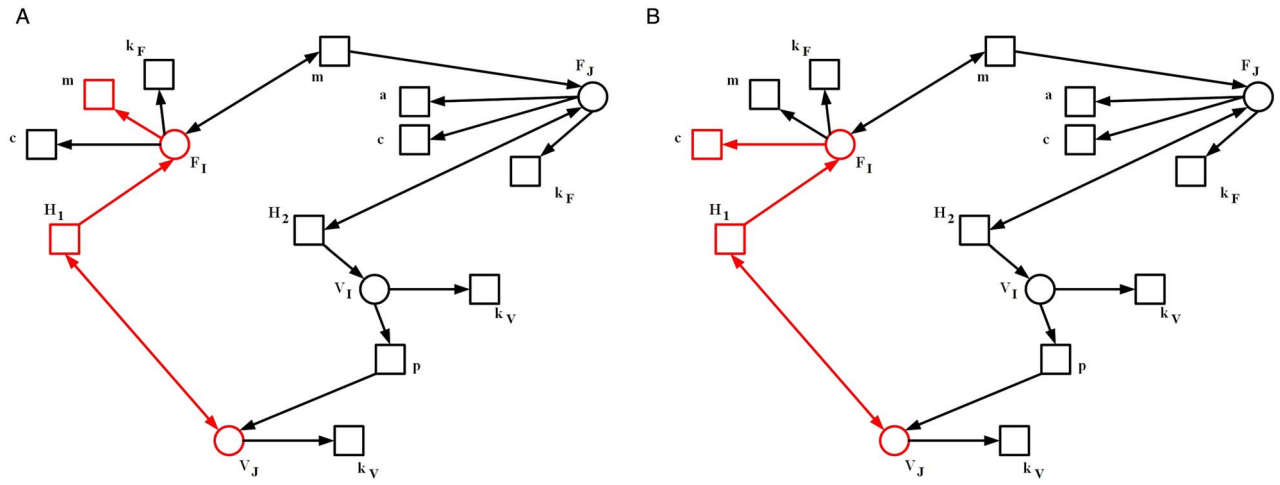


Fig. 6. PN modelling of the fox and vole interaction. Left panel presents the dynamics documented by the first term of equation (1) and the second term of equation (1). Right panel presents the dynamics documented by the second term of equation (1) and the fourth term of equation (1).

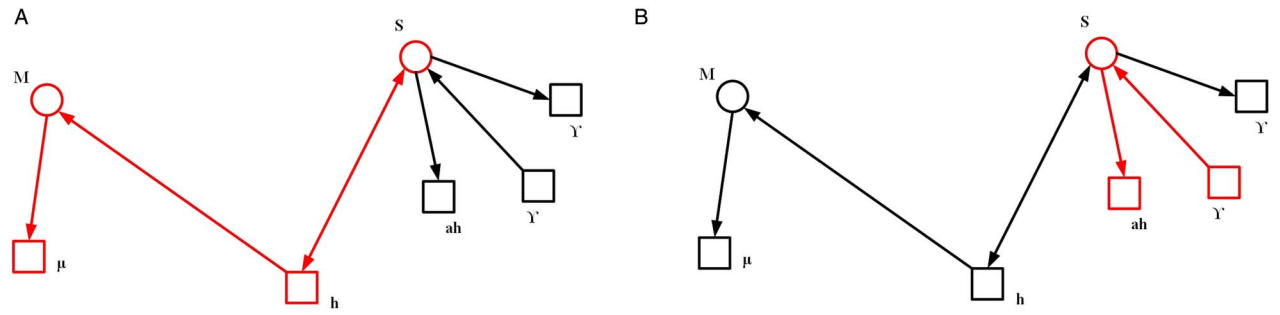


Fig. 7. Panel represent PN modelling of the fox and parasite interaction. Present equation (2). Right panel present PN modelling of the fox and parasite interaction. Presented the last two terms of equation (1).

found positive for *E. multilocularis* (Ali *et al.*, 2015). However, without DNA sequence analysis the results have some doubts.

We can see from the results that the number of infected fox cases decreased at a rate of three-fold to the initial cases reported. Thus, the control measures, when applied in a strategic manner, can help to in fact eradicate the disease spread. Based on the graphical interpretation, we can demonstrate the dynamics of the other three variables (infected vole and infectious fox & vole), in a similar manner. Two transition invariants (in Fig. 5 left panel) represent PN modelling of the fox and parasite interaction. This is mathematically depicted with the aid of equation (2), on the other hand, PN modelling of the fox and parasite interaction is presented in Fig. 6 right panel and is mathematically depicted by the last two terms of equation. (1). In a similar fashion, one can depict the correspondence between the dynamics interpreted in Fig. 7 and equations (1) and (2). Figure 8 and

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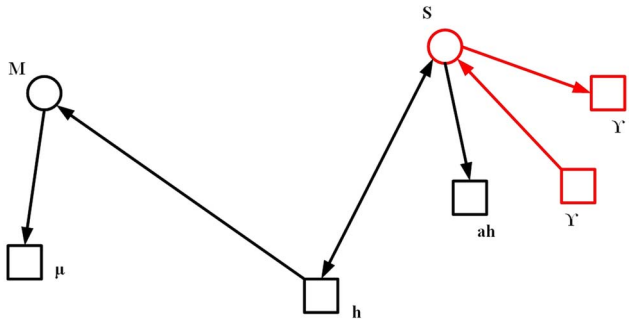


Fig. 8. PN modelling of the fox and parasite interaction. Presented the first two terms of equation (1).

the first two terms of equation (1) are in fact linked and actually provide the network for the fox and parasite interactions.

We emphasize that the disease modelling *via* PNs makes it easier to understand the interactions. Although in the recent literature, evidence is available that such techniques are used at cellular and molecular scales (Liu *et al.*, 2017; Wootton *et al.*, 2019), but no attempts have been made for the parasitology research. We therefore present here a novel approach. The system of differential equations and the PNs, together, work as a useful tool to explore the dynamical analysis in a more critical manner. From this study it is very obvious that the more variables are involved in computational framework (equations (1)–(4)) the better the results are in terms of forecasting, whereas, when fewer variables are involved (equations (5) and (6)), it is more challenging to forecast the infection spread and the impact of the control measures. The major advantage of this study is that both models can be visualized with the aid of networks. These networks and the corresponding invariants work as useful interpretation and forecasting tool. Such discrete tools can prove to be fruitful in future to design and plan the control measures, which will surely help to reduce the economic burden by controlling the spread of Echinococcosis.

Conclusions

These models present the interaction of two animals and prevalence of *E. multilocularis* in different regions and the *E. multilocularis* abundance in an animal host of different age groups. For prevention of the *E. multilocularis* we use control measures in this model, we conclude that for better administration of the disease, clear knowledge of the interactions between the two animals, as well as the respective densities, is required. There is a threshold, for which, the infectious fox density remains stable, in a control group. The purpose of this study is to provide a network analysis that can help to forecast such thresholds. In this paper we presented the transition invariants *via* a quantitative approach of PNs. This approach is recommended for future control measurements.

Financial support. The research is funded by NRPU 4275.

Conflict of interest. The authors declare that there is no conflict of interest or financial disclosure about this publication.

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