

McCaig C, Fenton A, Graham A, Shankland C & Norman R
(2013) Using process algebra to develop predator-prey models
of within-host parasite dynamics, *Journal of Theoretical
Biology*, 329, pp. 74-81.

This is the peer reviewed version of this article

NOTICE: this is the author's version of a work that was accepted for publication in Journal of Theoretical Biology. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in Journal of Theoretical Biology, [VOL 329 (2013)] DOI: <http://dx.doi.org/10.1016/j.jtbi.2013.03.001>

Author's Accepted Manuscript

Using process algebra to develop predator-prey models of within-host parasite dynamics

Chris McCaig, Andy Fenton, Andrea Graham, Carron Shankland, Rachel Norman



www.elsevier.com/locate/jtbi

PII: S0022-5193(13)00093-3
DOI: <http://dx.doi.org/10.1016/j.jtbi.2013.03.001>
Reference: YJTBI7236

To appear in: *Journal of Theoretical Biology*

Received date: 20 July 2012
Revised date: 30 January 2013
Accepted date: 4 March 2013

Cite this article as: Chris McCaig, Andy Fenton, Andrea Graham, Carron Shankland, Rachel Norman, Using process algebra to develop predator-prey models of within-host parasite dynamics, *Journal of Theoretical Biology*, <http://dx.doi.org/10.1016/j.jtbi.2013.03.001>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Using process algebra to develop predator-prey models of within-host parasite dynamics

Chris McCaig^{a,1}, Andy Fenton^b, Andrea Graham^c, Carron Shankland^d,
Rachel Norman^{e,*}

^a*Department of Computing Science and Mathematics, University of Stirling, Stirling, FK9 4LA, UK*

^b*Institute of Integrative Biology, University of Liverpool, L69 7ZB, UK*

^c*Department of Ecology and Evolutionary Biology, Princeton University, Princeton NJ, 08544, USA*

^d*Department of Computing Science and Mathematics, University of Stirling, Stirling, FK9 4LA, UK*

^e*Department of Computing Science and Mathematics, University of Stirling, Stirling, FK9 4LA, UK*

Abstract

As a first approximation of immune-mediated within-host parasite dynamics we can consider the immune response as a predator, with the parasite as its prey. In the ecological literature of predator-prey interactions there are a number of different functional responses used to describe how a predator reproduces in response to consuming prey. Until recently most of the models of the immune system that have taken a predator-prey approach have used simple mass action dynamics to capture the interaction between the immune response and the parasite. More recently Fenton and Perkins (2010) employed three of the most commonly used functional response terms from the ecological literature.

In this paper we make use of a technique from computing science, process algebra, to develop mathematical models. The novelty of the process algebra approach is to allow stochastic models of the population (parasite and immune cells) to be developed from rules of individual cell behaviour. By using this approach in which individual cellular behaviour is captured we have derived a ratio-dependent response similar to that seen in previous models of immune-mediated parasite dynamics, confirming that, whilst this type of term is controversial in ecological predator-prey models, it is appropriate for models of the immune system.

*Corresponding author.

Email address: ran@maths.stir.ac.uk (Rachel Norman)

¹Present address of Chris McCaig: Department of Mathematics and Statistics, University of Strathclyde, Livingstone Tower, 26 Richmond Street, Glasgow, G1 1XH, UK

1. Introduction

The immune system is made up a large number of different types of cells and proteins which interact in a highly complex way. Understanding how the immune system responds to parasites is a critically important problem in the fight against infectious diseases. Researchers have been using mathematical models to help us to understand these interactions for more than 30 years. There are a large number of publications in this area in which different models describe these interactions on many different scales and with differing levels of detail. For example, some people have developed large-scale (e.g., individual-based) models that describe explicitly the interactions between particular types of cells (e.g., the model of Ganusov *et al.* [18], that captures how IL-2 regulates the expansion of the CD4+T cell population). However, in order to analyse these models it is often necessary to rely on simulation rather than analytical solutions [32]. The disadvantage of this simulation-based approach is that the results depend on the values chosen for particular parameters and it is difficult to say anything general about the dynamical behaviour of the system. This is because an individual simulation considers only a single realisation of the stochastic model and it is only by performing a large number of simulations that we can comment more generally on the behaviour of the system even for one set of parameter values.

Other approaches take a more generic view and describe more biologically simplified interactions between ‘parasite’ and ‘immune’ cells [4, 30]. In this simplified context, a useful view is to assume that the immune cells behave like predators and the parasite cells behave like prey; this allows authors to borrow from ecological models of predator-prey systems. In these simplified models the interaction term between immune (I) and parasite (P) cells is often of the form $I.f(P)$. Ecological predator-prey models have made use of various functional responses [5, 8, 16, 21, 22] to describe the interaction between the two species. The functional response describes the rate at which a single predator consumes the prey species. In an immunological setting the functional response describes the rate at which a single immune cell removes parasites (whether directly or indirectly) and immunological models have focussed predominantly on simple mass action dynamics. One exception to this is a series of papers, Borghans and De Boer [10], Borghans *et al.* [11] and Pilyugin and Antia [31] which deployed a ratio-dependent functional response (so called because a predator’s consumption rate of prey depends on the numbers of predators and prey only through their ratio). This form of functional response has been the source of some controversy in the ecological literature. In 1992 a series of papers in a special edition of a journal were uniformly in favour of using ratio-dependent response to describe predator prey interactions e.g. [13]. However, in 1994 Abrams [1] responded to this by saying that this functional form did not reflect any plausible widely-applicable mechanism and was not supported by any available data. There is continued discussion about its use in the ecological context in the literature [1, 2, 3, 5, 6].

In the immunological context a ratio-dependent interaction rate has been ar-

rived at in a number of settings, by means of a quasi-steady-state approximation based on Michaelis-Menten dynamics used to describe biochemical interactions [31, 11]. This assumption is only valid for a certain range of parameters (for example it assumes a large amount of substrate relative to enzyme), although this can be extended by a change of variable [11].

A second alternative to the mass action assumption was recently discussed in Fenton and Perkins [17] who developed models of within-host interspecific parasite interactions making use of the three ecological functional responses described by Holling [21, 22]. In a model representing a single parasite species Fenton and Perkins made use of a generalised predator-prey model:

$$\begin{aligned}\frac{dP}{dt} &= rP - If(P), \\ \frac{dI}{dt} &= ef(P)I - \delta I,\end{aligned}\quad (1)$$

where P is the parasite, I is the immune response, r is the per capita growth rate of P , e is the rate at which immune proliferation is stimulated by contact with the parasite, δ is the decay rate of the immune response and $f(P)$ is the functional response. The three functional responses employed were

$$\begin{aligned}\text{Type 1: } f(P) &= \beta P, \\ \text{Type 2: } f(P) &= \frac{\beta P}{1 + h\beta P}, \\ \text{Type 3: } f(P) &= \frac{\beta P^2}{1 + h\beta P^2},\end{aligned}$$

where β is the rate at which parasites are killed and h is the handling time taken to process each parasite. It was found that (1) has quite different stability criteria for the three different functional responses. For a Type 1 functional response the model is neutrally stable; for Type 2 the model is always unstable; and for Type 3 the model stability criterion is $e > 2\delta h$. However, these functions were derived using a population-level approach, which seeks to describe changes in the numbers of different types of individuals in the population directly.

All of these models describe a population of cells within an individual, but make assumptions about how the cells interact at the cell population level. The advantage of these simplified models over the more biologically realistic simulation models is that they consist of coupled non-linear differential equations which can be analysed to determine the possible types of long-term behaviour and the ranges of parameter values under which they occur. This allows us to interpret results in very general terms and understand the relative importance of different parameters. However in modelling the immune system (and indeed many other systems) we would ideally like to write down rules about how individual cells behave and interact and derive the population-level behaviour directly from those individual level assumptions.

In this paper we present a technique which gives us the best of both worlds,

forming a natural bridge between these different scales: process algebra. This theoretical computer science technique is a family of related languages. They are suitable to describe systems comprised of many similar individual components, which may have complex interactions. The descriptions are abstract and concise, and underpinned by formal mathematical semantics. Process algebra allows us to write down rules of individual behaviour and then rigorously derive population-level equations. We can then carry out individual-based simulations as well as analyse the population-level equations. Process algebras are a theoretical computing science tool. Although initially developed to study distributed computer systems, more recently process algebras have been used to study biological systems [14, 33]. In particular the process algebra *Weighted Synchronous Calculus of Communicating Systems* (WSCCS) [37] has proven useful in studying a wide range of biological systems [19, 28, 27, 29, 35, 36]. Our group has established a rigorous method for deriving equations to describe the mean behaviour of an infectious disease system as a whole [28, 26]. This approach allows us to combine the benefits of ODEs and stochastic simulations.

Having previously established the use of this approach to study disease at the epidemiological (between-host) scale, we use WSCCS here to investigate predator-prey models of immune-mediated, within-host parasite dynamics. In this paper we wish to determine the form of the functional response in the population level equations that come from WSCCS models of the immune system, and compare it to the most commonly-used forms [17, 30, 12]. In this way we can investigate if any of the commonly used functional responses discussed above, or some novel form of functional response, emerge from a formal description of individual behaviour. This will allow us to establish whether WSCCS is a reasonable approach to modelling immunological systems, deriving population-level behaviour from assumptions about how individual cells interact.

2. Process algebra

The present work makes use of the process algebra WSCCS [37], which is a discrete time process algebra with each agent (here representing an individual immune cell or parasite) performing an action (representing some aspect of individual behaviour) in each step of time. These time steps are abstract: there is no notion of absolute time in WSCCS, only ordering of events. Time steps have no defined length, and therefore the modeller has freedom to capture events in each time step which happen with different durations. We describe different types of individual in the syntax of WSCCS and represent a population by the modular parallel composition of these agents.

Traditionally, process algebra models are analysed by deriving the underlying Markov chain of the model, by performing stochastic simulations or by algebraic manipulation of equivalences [7]. In recent years, the analysis of process algebra models by *fluid flow* approximation [15, 20, 26, 28] has become popular, i.e. rigorous derivation of population-level system dynamics, in the form of mean field equations or ordinary differential equations, from the individual-based process algebra model. This approach allows changing of scale, moving from the

stochastic description of individuals to a description of the mean behaviour of the population as a whole, considering only the syntax of the process algebra model: no lengthy complex computation is required. The automatic conversion between scales allows each perspective to be used in the strongest way possible. That is, individual observations formally generate the population-level model.

McCaig *et al.* [26] described a method to automatically derive mean field equations (MFEs) from WSCCS models. The translation is based on analysis of the potential actions of each agent in the context of the whole population, producing a term in the MFEs capturing change in the number of that agent. The translation from process algebra to mean field equations is based on a well known result, by Kurtz [23], for Markov chains. In this paper we develop a simple WSCCS predator-prey model of immune response to investigate the form of functional response that comes about from an individual-based description of the system.

2.1. WSCCS

In order to understand the model presented in Section 3, we remind the reader of the WSCCS language and the method of deriving mean field equations. The method was originally presented in [25]; the example here is new.

2.1.1. Syntax and Semantics

In WSCCS the basic components are *actions* and the *processes* (or *agents*) that carry out those actions. The actions are chosen by the modeller to represent activities in the system. For example, *infect*, *send*, *receive*, *throw dice*, and so on. The special pre-defined action \surd simply indicates the passing of time. Processes are constructed via a small number of operators, allowing ordering of actions, probabilistic choice between actions, and parallel composition of processes. The formal syntax and semantics of WSCCS is presented in Tofts [37], a portion of which is repeated in the appendix here for easy reference. In Figure 1 a simple model is presented to illustrate the language. This model, which was developed by McCaig *et al.* [25], describes ecological model of a population where growth depends on limited resource (density-dependent growth). In the model the density-dependence comes about through competition for food and the food is immediately replaced after being eaten.

The model defines five types of agents ($N1$ to $Popn$). The individuals in the population are modelled by the agents $N1$ and $N2$. The food resource for which individuals compete is modelled by the agents $F1$ and $F2$.

This is a two stage model reflecting two components of population dynamics. In the first stage, the individuals compete for food and reproduce if they are able to eat. In the second stage, individuals probabilistically ‘choose’ whether to die or not.

The process which can perform the action a and then evolve to process P is written $a : P$ where a is an action, and P a process. For example, the $F2$ process performs a \surd action and then becomes $F1$. Weighted (probabilistic) choice is expressed with the $+$ operator. For example, process $N2$ can die with

$$\begin{aligned}
N1 &\stackrel{\text{def}}{=} 1.eat : (N2 \times N2) + 1.\surd : N2 \\
F1 &\stackrel{\text{def}}{=} 1.\overline{eat} : F2 + 1.\surd : F2 \\
\\
N2 &\stackrel{\text{def}}{=} p_d.\surd : 0 + (1 - p_d).\surd : N1 \\
F2 &\stackrel{\text{def}}{=} 1.\surd : F1 \\
\\
Popn &\stackrel{\text{def}}{=} N1\{n\} \times F1\{f\}[\{\surd\}]
\end{aligned}$$

Figure 1: Naive growth model

probability p_d (and become the null process 0) or can survive with probability $1 - p_d$ (and become the process $N1$).

Communication occurs via the paired actions eat and \overline{eat} . These can be thought of as input and output respectively (so $F1$ outputs some food, and $N1$ may absorb that food). If an $N1$ does manage to eat then it reproduces, becoming two $N2$ agents in parallel (represented by the \times operator).

The system as a whole (described by $Popn$) comprises n individuals and f food items acting in parallel. WSCCS is a synchronous calculus: in every time step every agent has to perform some action (hence the \surd actions above — these processes are just marking time until the next stage). By combining simple known individuals in parallel, complex overall population level behaviour emerges.

2.2. Deriving Mean Field Equations

The semantics of WSCCS is transition-based, defining the actions that a process can perform and the weight with which a state can be reached. A problem WSCCS shares with all other process algebras is that of *state-space explosion*; i.e. the state space of a WSCCS description is exponential in the number of agents in that description. This problem is a serious bar to modelling biological problems as the number of individuals in most realistic systems is ideally in the thousands, if not millions, therefore methods of analysis requiring explicit generation of the state space are too computationally expensive, or even impossible.

Fluid-flow approximation provides a solution to this problem. For WSCCS McCaig *et al.* [26] presented an alternative and equivalent semantics is given for WSCCS in terms of Mean Field Equations. Algebraic rules are applied to the WSCCS syntax of the model to obtain a set of first-order difference equations expressing the *average* behaviour of the model. This is an approximation to the original transition-based semantics, but has been shown to be a close match with average results obtained from repeated simulations of the transition-based semantics [26]. There are four benefits to this approach. The state-space explosion problem is avoided. A new viewpoint of the system is produced, rigorously


```

function calculateTerm (A, w, a): String {
  case A in {
    probabilistic(A): return w * At;
    communicating(A):
      term = (At * collaborators(A))/(At + collaborators(A) + competi-
tors(A));
      if a equals √ return (A - term) else return term;
  }}

```

Figure 2: Pseudo code to calculate proportion of agents at time $t + 1$

and symbolically. The resulting MFE may be amenable to further algebraic analysis using standard mathematical techniques. Finally, and to the biologist most importantly, it is possible to exploit known (measured) information about individual behaviour and to link this with emergent population features. In other words, to use the semantics of process algebra to bridge automatically between the scales of individual behaviour and population properties.

The method is based around construction and interpretation of a table noting change in the number of agents in the system. The pseudo-code to compute these table entries based on the type of action carried out is repeated in Fig. 2. Some auxiliary definitions are required. The method is based on algebraic transformation of the syntax of the model. Processes can be classified by syntactic features as: *communicating* (having an action enabled that is involved in a communication), and *probabilistic* (having only actions enabled that are not involved in communication). For a process communicating on action a , we define two groups of agents involved in the synchronisation: *collaborators* are those processes with the matching action \bar{a} , and *competitors* are those processes with the same action a . We illustrate the method by deriving MFE for the simple growth model of Fig. 1.

2.2.1. Derivation of MFE for a Simple growth Model.

Consider again the simplistic growth model in Fig. 1. The MFE approximation uses the details of the actions in Fig. 1 to consider the evolution of numbers of agents. The table below shows rows relating to each agent, and each activity that agent can perform, and the resultant number of agents in the new state. For example, the row ($N1_t, eat$) details the evolution of $N1$ following an *eat* action. There is no entry under $F2$ (because $N1$ do not evolve to $F2$). The entry under $N2$ is calculated according to the code of Fig. 2 and the information that *eat* is a communicating action, collaborators in that action are $F1$ and there are no competitors. $F1$ evolves to $F2$ no matter which action occurs (indicating by *). The populated parts of the transition table for this system are as follows:

	$N2_{t+1}$	$F2_{t+1}$
$(N1_t, eat)$	$2 \times \frac{N1_t F1_t}{N1_t + F1_t}$	
$(N1_t, \sqrt{ })$	$N1_t - \frac{N1_t F1_t}{N1_t + F1_t}$	
$(F1_t, *)$		$F1_t$

Similarly, a table can be constructed for the evolution of $N2$ and $F2$ to $N1$ or 0 and $F1$ respectively.

	$N1_{t+1}$	$F1_{t+1}$	0
$(N2_t, \sqrt{ })$	$(1 - p_d)N2_t$		$p_d N2_t$
$(F2_t, \sqrt{ })$		$F2_t$	

Each column in each table can be used to construct a MFE for that agent. 0 is ignored here since this is not of interest to us. For example, using the first table, the following MFE are obtained

$$\begin{aligned}
N2_{t+1} &= 2 \times \frac{N1_t F1_t}{N1_t + F1_t} + N1_t - \frac{N1_t F1_t}{N1_t + F1_t} \\
&= N1_t + \frac{N1_t F1_t}{N1_t + F1_t} \\
F2_{t+1} &= F1_t,
\end{aligned} \tag{2}$$

where $N2_{t+1}$ represents the number of $N2$ agents at time $t + 1$ expressed in terms of $N1_t$, the number of $N1$ agents at time t . The second table generates different MFE

$$\begin{aligned}
N1_{t+2} &= (1 - p_d)N2_{t+1} \\
F1_{t+2} &= F2_{t+1}.
\end{aligned} \tag{3}$$

To obtain MFE for the system, equations (2) and (3) are combined, and simplified by removing intermediate terms, i.e. $N2$, and $F2$, to yield an expression of N at time t . We also simplify by collapsing the two time steps above into one time step. The resulting MFE become

$$\begin{aligned}
N_{t+1} &= (1 - p_d)N_t + (1 - p_d) \frac{N_t F_t}{N_t + F_t} \\
F_{t+1} &= F_t,
\end{aligned} \tag{4}$$

We can further simplify by noting that the amount of food doesn't change so that we can write $F_{t+1} = F_t = f$. Substituting f for the F 's in (4) we can

simplify to have a single equation that describes the population:

$$N_{t+1} = (1 - pd)N_t + (1 - pd)\frac{N_t f}{N_t + f}.$$

3. Model

The model considered in this section is inspired by the predator-prey micro-parasite model of Fenton and Perkins (2010) summarised earlier. Here we give a description of the individual behaviour modelled and also the MFEs that are derived from the models. The WSCCS description of the model can be found in Fig. 3.

$$\begin{array}{l}
 P1 \stackrel{\text{def}}{=} p_{pp} \cdot \sqrt{} : P2 \times N2 + (1 - p_{pp}) \cdot \sqrt{} : P2 \\
 I1 \stackrel{\text{def}}{=} p_{di} \cdot \sqrt{} : 0 + (1 - p_{di}) \cdot \sqrt{} : I2 \\
 \\
 P2 \stackrel{\text{def}}{=} 1 \cdot \text{phag} : 0 + 1 \cdot \sqrt{} : P1 \\
 I2 \stackrel{\text{def}}{=} 1 \cdot \overline{\text{phag}} : I1 \times I1 + 1 \cdot \sqrt{} : I1 \\
 N2 \stackrel{\text{def}}{=} 1 \cdot \sqrt{} : P1 \\
 \\
 Popn \stackrel{\text{def}}{=} P1\{p\} \times I1\{i\}[\{\sqrt{}\}]
 \end{array}$$

Figure 3: Simple predator-prey type immunology model

Here we focus on illustrating the development and application of the process algebra approach with reference to a highly simplified, generic parasite-immune system interaction. This framework can readily be extended to incorporate more realistic features and complexities seen in genuine host-parasite systems. In our model there are two types of individual: I , representing immune cells, and P , representing parasites, e.g. malaria or giardia. The model develops in two separate stages which together form one “time step”. In the first stage of the model the parasite cells proliferate, with probability p_{pp} , dividing to give rise to a new parasite cell, N , which is not able to be neutralised by the immune response in the next stage of the model. At the same time the immune cells can die, with probability p_{di} , or continue on to the next stage of the model. In the second stage of the model parasite cells that come into contact with an immune cell are phagocytosed. As a result of phagocytosis, parasite cells are removed from the system and immune cells proliferate, becoming two cells in the next iteration of the model. In addition, the new parasites, N , become P in the next iteration of the model.

Over the two stages we have moved from a population featuring only I and P , to a system consisting of these same types of individuals, but in different

numbers. It is the mean of this change in the numbers of I and P that is captured in our MFEs. The MFEs derived from this model, using the algorithm of McCaig *et al.* [26] as described above, are:

$$\begin{aligned} P_{t+1} &= (1 + p_{pp})P_t - \frac{P_t(1 - p_{di})I_t}{P_t + (1 - p_{di})I_t}, \\ I_{t+1} &= (1 - p_{di})I_t + \frac{P_t(1 - p_{di})I_t}{P_t + (1 - p_{di})I_t}. \end{aligned} \quad (5)$$

In contrast to the three types of functional response used by Fenton and Perkins (2010), which are all functions of P only, this model features a functional response that is a function of both P and I :

$$f(P, I) = \frac{P_t(1 - p_{di})}{P_t + (1 - p_{di})I_t}. \quad (6)$$

This is the ratio-dependent functional response, which is similar to those which have derived before for within-host parasite dynamics by a quasi-steady-state assumption [10, 11, 31] and has been more widely used in an ecological context [1, 2, 3, 5, 6]. Here we have found this functional response emerging naturally from the simple individual behaviour described in our process algebra model.

3.1. Analysis of the models

Our WSCCS model has the advantage over other approaches that it can be studied either by performing simulations, or by producing time series of the MFEs that describe the average behaviour. For this model we find that for many sets of parameter values the total number of parasites grows exponentially, and consequently stochastic simulations are very computationally expensive. For this reason, the results described here were obtained by producing time series of the MFEs. This illustrates one of the advantages of this approach; even in situations where performing stochastic simulations of the model is impractical (because of large numbers of individuals) we can easily determine the average behaviour of the system, and be sure that it is a direct consequence of the heterogeneous individual behaviours described.

The model presented here features only two parameters, both of which are probabilities (p_{pp} , the probability of parasite proliferation, and p_{di} , the probability of immune cell death), so it is possible to obtain results across the entire range of the parameter space. Stability analysis showed that stability depends on the initial ratio of $\rho = I/P$ and whether $I \rightarrow 0$ or $P \rightarrow 0$ first. We therefore produced time series of (5) across the parameter space, for small initial values of I and P and for different values of the initial ratio $\rho = I_1/P_1$. The absolute numbers of I_1 and P_1 are not important in terms of the qualitative results; the shape of the curves in the resulting graphs are set purely by the ratio ρ . We illustrate this in Fig. 4 by showing time series for $\rho = 1$ with different initial conditions (P always initially equal to I), which shows that the speed of clearance of the parasite is not affected by an increase in the initial infection load if

the initial number of immune cells are increased by the same factor.

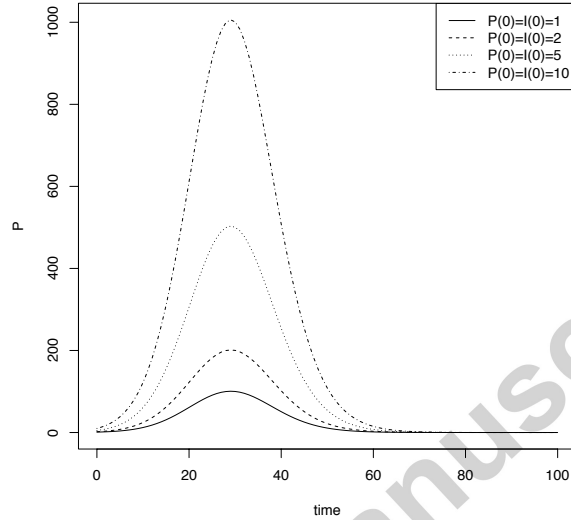


Figure 4: P with fixed $\rho = 1$ for different initial values of $P = I$: $p_{pp} = 0.8$, $p_{di} = 0.1$

Across the parameter space we can classify several different types of dynamical behaviour, though the range of different types of behaviour varies depending on the ratio ρ . We present plots of the boundaries of the different types of behaviour for three different values of ρ (Figs. 5-7), with up to eight different types of behaviour in the regions labelled as follows:

- A - A small and short-lived increase in the number of immune cells, followed by decrease of I to 0, while the number of parasites is decreasing for the whole of the duration studied (10^4 time steps).
 - B - I and P both decrease from the beginning.
- A and B represent the situation where an initial infection is swiftly removed from the host by the immune response ($P \rightarrow 0$).
- C - Both I and P increase initially but ultimately both tend to 0. This represents the situation where the parasite becomes established, possibly causing illness, but ultimately the immune response is able to clear it.
 - D - I and P are both increasing for the entire duration studied.
 - E - I is decaying from the beginning while P experiences unbounded growth.

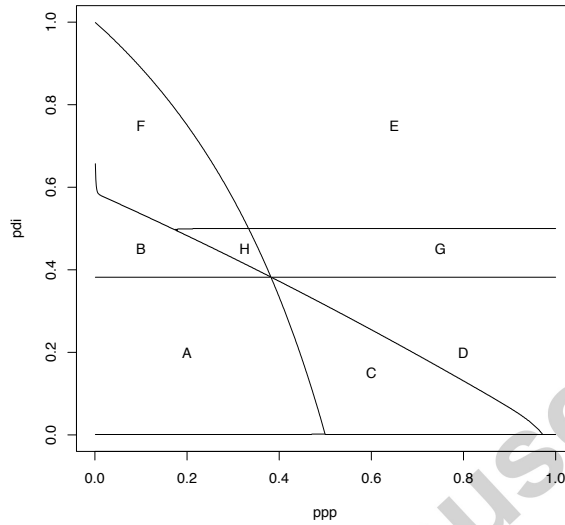


Figure 5: Parameter space for $\rho = 1$

- F - I is decaying from the beginning while P experiences a small, short-lived drop but ultimately experiences unbounded growth.

For most of E and F in all of the conditions considered here $p_{di} > 0.5$. This means that immune cells are more likely to die than survive and possibly proliferate, therefore the immune cells can never increase in number.

- G - P increases from the beginning while I experiences a small, short-lived drop but ultimately experiences unbounded growth.
- H - Both I and P experience a small, short-lived drop but both ultimately experience unlimited growth.

D, E, F, G and H represent the situation where the parasite overwhelms the host's immune system, ultimately leading to host death. Hence, the diagonal line separating these regions from regions A-C represents the threshold separating parasite persistence and growth from parasite eradication (effectively, it is the within-host equivalent to the $R_0=1$ threshold line inherent in standard between-host disease ecology, for parasite persistence).

Fig. 5 is the parameter space for $\rho = 1$. Here all of the types of behaviour described are possible in different areas of the parameter space.

For different values of the ratio ρ similar results are found, but with some of the regions increased in size and some reduced or no longer present. For

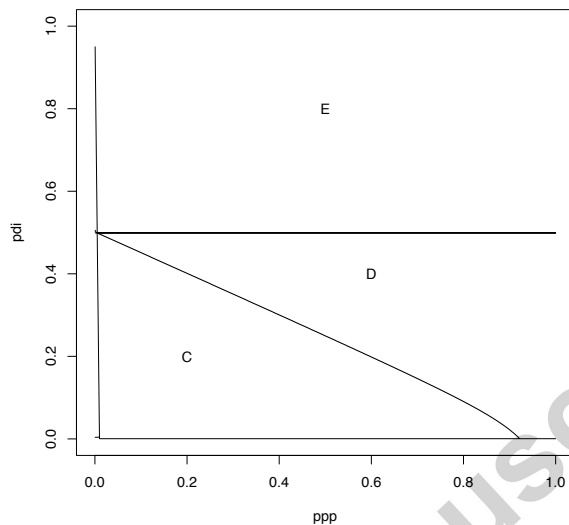


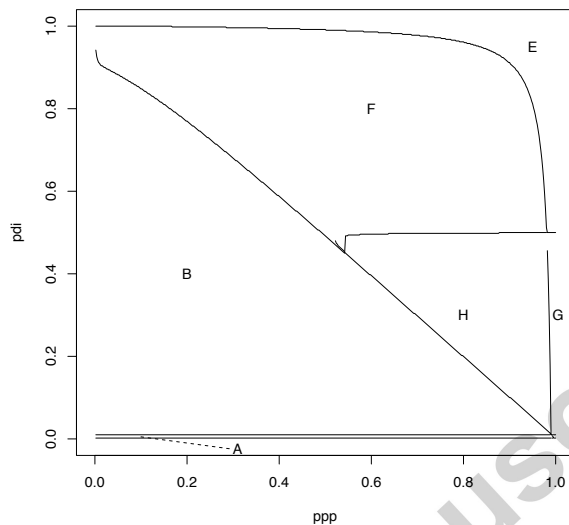
Figure 6: Parameter space for $\rho = 0.01$

instance Fig. 6 features the parameter space for $\rho = 0.01$. We see here that for this small value of ρ (initially many more parasites than immune cells) regions A and B, where the parasite is controlled from the beginning of the infection, do not feature and P always increases initially.

Conversely we can consider the parameter space for $\rho = 100$ (Fig. 7). We can see that for this large value of ρ (initially many more immune cells than parasites, possibly reflecting the scenario of an existing immune memory to the parasite) region C is not present, meaning that there is never an outbreak of the disease that becomes established (P increases) but is ultimately controlled by the immune system. Instead either the parasite kills the host (E, F and H) or the immune response suppresses the parasite (B). The only situations where P can increase is when p_{pp} is large (the parasites proliferate rapidly) or where p_{di} is large (immune response dies out before it can attack the parasite).

4. Conclusions

In this paper we have presented a predator-prey model of immune-mediated, within-host parasite dynamics, developed using the process algebra WSCCS. We have found that the mean field equations, which capture the average behaviour of the model, feature a functional response term that does not simply depend on the density of parasite or immune cells, but on their ratio. A similar functional form has been deployed in ecological predator-prey models [5], and is similar

Figure 7: Parameter space for $\rho = 100$

to those found by other authors who have modelled general immune responses with handling time [31], or T cell proliferation [12]. In these papers the authors assume that parasite and immune cells interact like a substrate and enzymes respectively in biochemical interactions and follow Michaelis-Menten kinetics. They also use a quasi-steady-state assumption. This means that a number of assumptions have to be made, including the random mixing of cells (mass action), that there are initially a large number of parasite cells and that these parasite cells reach equilibrium faster than new immune cells are formed. In the approach presented here we also assume random mixing (although we could relax that assumption in later models which the previously discussed approaches could not). The mean field assumptions hold when the populations of cells are large, but we can determine what happens at small population densities by carrying out stochastic simulations of the system. We do not have to make any assumptions about the speed at which equilibrium is reached. The results presented here give support to the use of ratio-dependent interactions in an immune system even for very simple assumptions about individual cell behaviour. Although similar results might be gained using the quasi-steady-state assumption the advantage that process algebra gives is the ability to build more complex models in the future, for example previous work has added time delays, spatial factors and partitioning of the population [9]. Process algebra also allows us to use a mix of stochastic individual based simulations and mean field equations in order to analyse the system under consideration.

In the case presented here, by carrying out the analysis presented in 3.1 we can look at all of the possible dynamical behavior of this simple parasite-immunity system. We see that the qualitative dynamics are unaffected by size of the initial populations, with the shapes of plots of the time series determined solely by the initial ratio of immune cells to parasites. Quantitatively, changing the size of the initial population, while maintaining the ratio I/P (as in Fig. 4), changes the size of both sub-populations for the entire duration studied, by the same proportion.

Time series of the MFEs were produced for three different ratios of the initial conditions across the entire parameter space. Depending on the initial conditions the range of behaviour seen across the parameter space is different. This might represent exposure to different doses of parasites (which changes P) or previous exposure to the pathogen, or vaccination which would increase I . For equal initial numbers of parasites and immune cells there is a wide range of different types of behaviour from the immune cells immediately overwhelming the parasite cells, to a short increase in parasite cells before they are controlled, to parasite cells overwhelming the immune cells and growing exponentially. In the situation where there are initially many more parasites than immune cells (representing the situation where the host is exposed to a large dose of an infection) the parasite load always grows initially, though for lower values of both parameters the infection is ultimately cleared. This could correspond, for instance, to the situation where a host is re-exposed to a known pathogen. Secondary immunity developed during the initial exposure can be so effective that the host does not become unwell. Conversely when there are initially many more immune cells than parasites there is no region of parameter space in which the parasite load initially increases but is ultimately controlled. If the parasite ever becomes established it will grow exponentially, leading to host death. These behaviours seem intuitively obvious for the simple type of infection presented here but are very different to the sort of behaviour found in Fenton and Perkins (2010). In particular they found cycles, from models which made use of Type 2 and Type 3 functional responses. For most types of viral or bacterial infection, once an infection is cleared we would only see re-emergence of the infection if the host is re-exposed, and often only if the secondary infection was with a different strain of the parasite. This means that cycles are not a realistic behaviour for the sort of simple infection being considered. Immune memory [34] means that when re-infected with a known parasite there would initially be more immune cells than parasites in our simple model. We therefore believe that the model we have derived here is realistic for a broad range of infections.

We have already shown in previous work that process algebra can give us useful insights into host-pathogen interactions [24, 25, 26, 27]. In this work process algebra has shown an important insight into the interaction of the immune system and a simple parasite. By describing simple interactions at the individual level we obtain equations to describe the population that feature a functional response which is similar to, and gives weight to other models of the immune system [12, 31, 11]. It should be noted, however, that not all types of parasite, nor all types of immunity, behave in the way described by the simple model

presented here. The work presented here provides an essential proof of concept, allowing subsequent work to explore the consequences, at the population level, of introducing more complex rules at the individual level (e.g. antigenic variation of parasites or affinity maturation of B cell), where those population-level consequences are unknown beforehand.

Hence, the work presented here has shown that process algebras are a promising approach for this sort of problem.

Appendix A. Syntax and Semantics of WSCCS

The possible WSCCS expressions are given by the following BNF grammar:

$$A ::= X \mid a:A \mid \Sigma\{w_i.A_i \mid i \in I\} \mid A \times B \mid A[L \mid \Theta(A) \mid A[S] \mid X \stackrel{\text{def}}{=} A.$$

Here $X \in \text{Var}$, a set of process variables; $a \in \text{Act}$, an action group; $w_i \in \mathscr{W}$, a set of weights; S a set of renaming functions, $S : \text{Act} \rightarrow \text{Act}$ such that $S(\surd) = \surd$ and $S(a) = S(\bar{a})$; action subsets $A \subseteq \text{Act}$ with $\surd \in A$; and arbitrary indexing sets I . Actions form an abelian group with identity \surd and the inverse of action a being \bar{a} . Actions occur instantaneously and have no duration.

The informal interpretation of the operators is as follows:

- 0 a process which cannot proceed, representing deadlock ;
- X the process bound to the variable X ;
- $a:A$ a process which can perform the action a becoming the process A ;
- $\Sigma\{w_i.A_i \mid i \in I\}$ the weighted choice between processes A_i , the weight of A_i being w_i . Considering a large number of repeated experiments of this process, we expect to see A_i chosen with relative frequency $w_i / \sum_{i \in I} w_i$. Weights are generally positive natural numbers or reals, but may also incorporate the special weight ω which is greater than all natural numbers. This is used in *priority* and is written $m\omega^n$ where $m, n \geq 0$. The binary plus operator can be used in place of the indexed sum, i.e. writing $\Sigma\{1_1.a:0, 2_2.b:0 \mid i \in \{1, 2\}\}$ as $1.a:0 + 2.b:0$;
- $A \times B$ the synchronous parallel composition of A and B . At each stage each process must perform an action with the composed process performing the composition (denoted $\#$) of the individual actions, e.g. $a:A \times b:B$ yields $a\#b:(A \times B)$. This is a powerful operator: models are constructed by describing simple individuals and composing a number of those in parallel. McCaig [24] introduced an extended notation $A\{n\}$ which is syntactic sugar for n instances of process A in parallel, where $n \in \mathbb{N}$;
- $A[L$ a process which can only perform actions in the group L . This operator is used to enforce communication on actions $b \notin L$. Two processes in parallel may communicate when one carries out an action and the other carries out the matching co-action, e.g. eat and \bar{eat} . Communication can

$a:A \xrightarrow{a} A$	$\sum \{w_i \cdot A_i \mid i \in I\} \xrightarrow{w_i} A_i$
$\frac{A \xrightarrow{a} A' \quad B \xrightarrow{b} B'}{A \times B \xrightarrow{a\#b} A' \times B'}$	$\frac{A \vdash^w A' \quad B \vdash^v B'}{A \times B \vdash^{wv} A' \times B'}$
$\frac{A \xrightarrow{a} A' \quad B \vdash^w B'}{A \times B \vdash^w A' \times B'}$	$\frac{A \vdash^w A' \quad B \xrightarrow{a} B'}{A \times B \vdash^w A' \times B}$
$\frac{A \xrightarrow{a} A' \quad a \in L}{\text{does}_L(A)}$	$\frac{A \vdash^w A' \quad \text{does}_L(A')}{\text{does}_L(A)}$
$\frac{A \xrightarrow{a} A' \quad a \in L}{A \upharpoonright L \xrightarrow{a} A' \upharpoonright L}$	$\frac{A \vdash^w A' \quad \text{does}_L(A')}{A \upharpoonright L \vdash^w A' \upharpoonright L}$
$\frac{A \xrightarrow{a} A'}{A[S] \xrightarrow{S(a)} A'[S]}$	$\frac{A \vdash^w A'}{A[S] \vdash^w A'[S]}$
$\frac{A \xrightarrow{a} A' \quad X \stackrel{\text{def}}{=} A}{X \xrightarrow{a} A'}$	$\frac{A \vdash^w A' \quad X \stackrel{\text{def}}{=} A}{X \vdash^w A'}$
$\frac{A \xrightarrow{a} A'}{\Theta(A) \xrightarrow{a} \Theta(A')}$	$\frac{A \xrightarrow{n\omega^i} A' \nexists (j > i) \cdot A \xrightarrow{m\omega^j} A''}{\Theta(A) \xrightarrow{n} \Theta(A')}$

Table A.1: Operational rules for WSCCS

be used to model passing of information from one process to another, or to coordinate activity. Such communication is strictly two-way; that is, only two processes may interact on this action ;

- $\Theta(A)$ represents taking the prioritised parts of the process A only (we do not use prioritised communication in this paper, but it is included for completeness) ;
- $A[S]$ represents A relabelled by the function S (we do not use relabelling in this paper, but it is included for completeness) ;
- $X \stackrel{\text{def}}{=} A$ represents binding the process variable X to the expression A .

The semantics of WSCCS is transition based, defining the actions that a process can perform and the weight with which a state can be reached. The operational rules of WSCCS, presented in Table A.1, formalise the descriptions above. In particular note the two different arrows which feature in the table: \xrightarrow{a} represents a transition associated with the action a ; and \vdash^w represents a transition associated with a weight w . The auxiliary predicate $\text{does}_L(A)$, which denotes the ability of A to perform L after zero or more probabilistic actions, is well defined since only finitely branching choice expressions are allowed.

Acknowledgements

This work was supported by EPSRC through *System Dynamics from Individual Interactions: A process algebra approach to epidemiology* (EP/E006280/1, CM, CS and RN 2007-2010) and by the University of Stirling.

- [1] P. Abrams (1994). The fallacies of ratio-dependent predation. *Ecology*, 75:1842–1850.
- [2] P. Abrams (1997). Anomalous predictions of ratio-dependent models of predation. *Oikos*, 80:163–171.
- [3] P. Abrams and L. Ginzburg (2000). The nature of predation: prey dependent, ratio dependent or neither? *Trends in Ecology & Evolution*, 15:337–341.
- [4] R. Antia and M. Lipsitch (1997). Mathematical models of parasite responses to host immune defences *Parasitology*, 115 S S155–S167
- [5] R. Arditi and L. Ginzburg (1989). Coupling in predator prey dynamics - ratio-dependence *Journal of Theoretical Biology*, 139:311-326.
- [6] R. Arditi and L. Ginzburg (2012). *How Species Interact. Altering the Standard View on Trophic Ecology*. Oxford University Press, Oxford, UK.
- [7] J.C.M. Baeten (2005) A brief history of process algebra. *Theoretical Computing Science*, 335(2/3):131–146.
- [8] J.R. Beddington (1975). Mutual interference between parasites or predators and its effect on searching efficiency. *Journal of Animal Ecology*, 51:331–340.
- [9] S. Benkirane (2011). Process algebra for epidemiology: evaluating and enhancing the ability of PEPA to describe biological systems *Thesis*, <http://hdl.handle.net/1893/3603>.
- [10] J.A.M. Borghans and R.J. De Boer (1995). A minimal model for T-cell vaccination. *Proceedings of the Royal Society of London Series B*, 259:173–178.
- [11] J.A.M. Borghans, R.J. De Boer and L.A. Seegel (1996). Extending the quasi-steady state approximation by changing variables. *Bulletin of Mathematical Biology*, 58(1), 43–63.
- [12] R.J. De Boer and A.S. Perelson (1995). Towards a General Function Describing Cell Proliferation. *Journal of Theoretical Biology*, 175, 567-576.
- [13] L.B. Slobodkin (1992). A summary of the special feature and comments on its theoretical context and importance. *Ecology*, 73, 1564-1566.

- [14] M. Calder, S. Gilmore and J. Hillston (2006). Modelling the influence of RKIP on the ERK signalling pathway using the stochastic process algebra PEPA. *Transactions on Computational Systems Biology VII*, 4230:1–23.
- [15] L. Cardelli. On process rate semantics. *Theoretical Computer Science*, 391:190–215, 2008.
- [16] D.L. DeAngelis, R.A. Goldstein and R.V. O’Neill (1975). A model for trophic interaction. *Ecology*, 56:881–892.
- [17] A. Fenton and S. E. Perkins (2010). Applying predator-prey theory to modelling immune-mediated, within-host interspecific parasite interactions. *Parasitology*, 137:1027–1038.
- [18] V.V. Ganusov, D. Milutinovic and R.J. De Boer (2007). IL-2 regulates expansion of CD4(+) T cell populations by affecting cell death: Insights from modeling CFSE data, *Journal of Immunology* 179(2), 950–957.
- [19] M.J. Hatcher and C. Tofts (1995). The evolution of polygenic sex determination with potential for environmental manipulation. Technical Report UMCS-95-4-2, Department of Computer Science, University of Manchester.
- [20] J. Hillston. Fluid Flow Approximation of PEPA models. In *QEST’05, Proceedings of the 2nd International Conference on Quantitative Evaluation of Systems*, pages 33–42. IEEE Computer Society Press, Torino, September 2005.
- [21] C.S. Holling (1959a). The components of predation as revealed by a study of small mammal predation of the European pine sawfly. *Canadian Entomologist*, 91:293–320.
- [22] C.S. Holling (1959b). Some characteristics of simple types of predation and parasitism. *Canadian Entomologist*, 91:358–398.
- [23] T.G. Kurtz (1970). Solutions of ordinary differential equations as limits of pure jump markov processes. *Journal of Applied Probability*, 7:49–58.
- [24] C. McCaig (2007). From Individuals to Populations: changing scale in process algebra models of biological systems. PhD thesis, University of Stirling (2008) Available from <http://hdl.handle.net/1893/398>
- [25] C. McCaig, R. Norman, and C. Shankland (2008). Process Algebra Models of Population Dynamics. In *Algebraic Biology*, volume 5147 of *Lecture Notes in Computer Science*, 139–155, Springer-Verlag.
- [26] C. McCaig, R. Norman, and C. Shankland (2011a). From Individuals to Populations: a mean field semantics for process algebra. *Theoretical Computer Science*, 412(17), 1557–1580, doi:10.1016/j.tcs.2010.09.024.

- [27] C. McCaig, M. Begon, R. Norman and C. Shankland (2011b). A Symbolic Investigation of Superspreaders. *Bulletin of Mathematical Biology*, 73(4), 777–794.
- [28] C. McCaig, R. Norman, and C. Shankland (2009). From individuals to populations: A symbolic process algebra approach to epidemiology. *Mathematics in Computer Science*, 2(3):535–556.
- [29] R. Norman and C. Shankland (2003). Developing the use of process algebra in the derivation and analysis of mathematical models of infectious disease. In *Computer Aided Systems Theory - EUROCAST 2003*, volume 2809 of *Lecture Notes in Computer Science*, pages 404–414. Springer-Verlag.
- [30] M.A. Nowak and R.M. May (2000). *Virus dynamics: Mathematical Principles of Immunology and Virology*. Oxford University Press, Oxford, UK.
- [31] S.S. Pilyugin and R. Antia (2000). Modelling immune responses with handling time. *Bulletin of Mathematical Biology*, 62, 869–890.
- [32] M. Precharattana, A. Nokkeaw, W. Triampo, D. Triampo and Y. Lenbury (2011). Stochastic cellular automata model and Monte Carlo simulations of CD4(+) T cell dynamics with a proposed alternative leukapheresis treatment for HIV/AIDS *Computers in Biology and Medicine*, 41(7), 546–558, DOI: 10.1016/j.combiomed.2011.05.005.
- [33] A. Regev, E.M. Panina, W. Silverman, L. Cardelli and E. Shapiro (2004). Bioambients: an abstraction for biological compartments. *Theoretical Computer Science*, 325:141–167.
- [34] F. Sallusto, D. Lenig, R. Forster, M. Lipp and A. Lanzavecchia (1999). Two subsets of memory T lymphocytes with distinct homing potentials and effector functions *Nature*, 401:708–712
- [35] D.J.T. Sumpter and D.S. Broomhead (2001). Relating individual behaviour to population dynamics. *Proceedings of the Royal Society of London Series B*, 268:925–932.
- [36] C. Tofts (1993). Using process algebra to describe social insect behaviour. *Transactions of the Society for Computer Simulation*, 9:227–283.
- [37] C. Tofts (1994). Processes with probabilities, priority and time. *Formal Aspects of Computing*, 6:536–564.

Highlights

- Population level dynamics were derived from the interactions of parasite and immune cells.
- Interactions between parasites (P) and immune cells (I) should be of ratio-dependent form
- This is in contrast to previous models with commonly used predator-prey functional responses.
- The derived model gives realistic population dynamics.

Accepted manuscript