

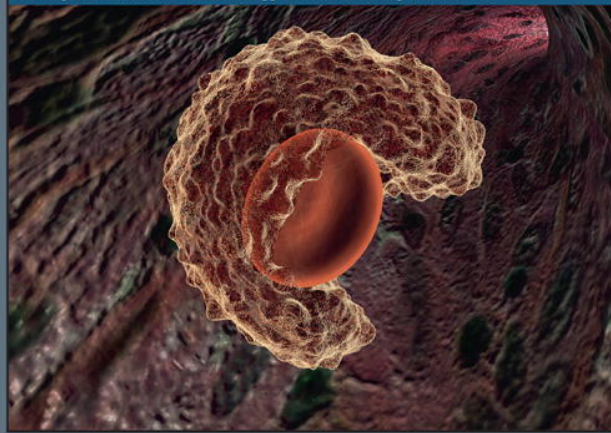


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Information
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Report

Dealing with software viruses: A biological paradigm

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A B S T R A C T

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We introduce a probability model for populations of cells and viruses that interact in the presence of an anti-viral agent. Cells can be infected by viruses, and their longevity and ability to avoid infection are modified if they survive successive attacks by viruses. Viruses that survive the effect of the anti-viral agent may find that their ability to survive a future encounter with molecules of the anti-viral agent is modified, as is their ability to infect a healthy cell. Additionally, we assume that the anti-viral agents can be a cocktail with different proportions of agents that target different strains of the virus. In this paper, we give the state equations for the model and derive its analytical solution in steady state. The solution then provides insight into the appropriate mix or “cocktail” of anti-viral agents that can be designed to deal with the virus’ ability to mutate. In particular, the analysis shows that the concentration of anti-viral agent by itself does not suffice to ultimately control the infection, and that it is important to dose a mix of anti-viral agents so as to target each strain of virus in a specific manner, taking into account the ability of each virus strain to survive in the presence of the anti-viral agents. Models of this kind may eventually lead to the computer aided design of therapeutic protocols or drug design.

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1. Introduction

Mathematical models of populations have long been of interest in biology (May and Hassell, 1988). They have been applied successfully to the study of infectious diseases (Bonhoeffer et al., 1997), and have even been popularised in a recent novel (Haddon, 2004). In computer science and electrical engineering, stochastic models of “populations” of telephone calls, computer network packets and computer systems (Kelly, 1978; Gelenbe and Mitrani, 1980) have received considerable attention, while the study of natural and artificial neural networks has also provided a fruitful connection between models of interest to biology and their counterparts in engineering (Rumelhart et al., 1986; Gelenbe, 1993). Similarities between

performance models for parallel computation (Gelenbe, 1989) and mathematical models of food chains (Cohen et al., 1990) in biology have also been pointed out.¹ Furthermore, population models (Galton and Watson, 1874), as well as the study of telephone calls (Kolmogorov, 1931) which gave rise to queueing theory (Asmussen, 1987; Gelenbe and Fournau, 2002), have had significant impact on the development of the mathematics of random processes (Medhi, 1994).

In this paper, we consider a stochastic population model which is inspired by both engineering and biological considerations. The biological context we have in mind corresponds to an environment containing a concentration of viruses of healthy and infected agents, and of an active anti-viral agent. The engineering context we consider comes from computer

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software, where “intelligent agents” interact in accomplishing different tasks. In particular, there are harmful software agents such as computer viruses and worms. They infect and degrade the software of *bona fide* users, and can be eliminated by a specific anti-virus agent designed to block or destroy software viruses. In the terminology used throughout this paper, we will only refer to the biological paradigm, so as to avoid going back and forth between these motivating examples.

The biological agents we consider are replenished through external migration or agent division, by the production of viruses by infected agents, by the transformation of normal agents into infected agents through their encounter with viruses, and by mutation. Viruses may be rendered inactive by their encounter with molecules of the anti-viral agents. However, a virus may survive the encounter with the anti-viral agent and mutate into a hardier or different strain. All of these entities can also be naturally eliminated from this environment, for instance by the death of healthy and infected agents, by the diffusion of all these entities out of the medium being considered, and through the combination of these different entities as a result of their interaction.

Thus healthy agents too may belong to different types or strains which affect their level of resistance to infection and their longevity. Viruses also can belong to different strains in order to represent their degree of virulence and their ability to resist to the anti-viral agent. Our model can also represent types of agents whose resistance is modified by successive encounters with viruses, either because they become more resistant, or less resistant. The variation of an agent's resistance to encounters with viruses can also be a non-monotone function of the number of encounters, e.g. an increasing resistance, followed at some point by a decreasing resistance as the number of encounters increases.

A virus' encounter with an agent may or may not be “successful” from the virus' perspective by resulting, or not resulting, in the agent's infection. After the encounter we assume that the virus is either incorporated into the infected agent, or that it is eliminated by the agent if the agent does not become infected. In either case, the virus involved in the encounter disappears as an entity (i.e. is destroyed by the agent or is incorporated into it), and either the original agent remains healthy, or in case of infection the original agent becomes an infected agent.

The main result of this paper is to show that under appropriate assumptions, a stochastic model of the size of such a biological mix of populations can lead to a steady-state solution which has a particularly simple product form, in which the joint probability distribution of the size of each sub-population is expressed as the product of the marginal distribution of each population. These marginal probabilities are themselves computed from the solution of a set of non-linear equations. We then show how this result can apply to a special case, so as to provide insight in the manner in which the anti-viral agent should be composed of a “cocktail” each of whose elements must be targeted in a specific manner to each strain of the mutating virus so as to keep the viral population under control.

2. The mathematical model

We model the numbers of each of the four entities, namely the numbers of viruses and agents, and the number of molecules of anti-viral agents at some time $t \geq 0$, or their concentrations, with the following variables:

- The number of healthy agents of type or strain i is represented by a natural number $C_i(t) \geq 0$, where $i = 0, 1, 2, \dots$. The strain of the agent can impact the degree to which it becomes infected, and its survivability or longevity.
- The number of infected agents (or their concentration) is also represented by a natural number $\iota(t) \geq 0$. In this paper, we do not distinguish between the strains of infected agents.
- $a(t) \geq 0$ is the quantity or concentration of the anti-viral agent, and is also a natural number.
- Finally, $V_j(t) \geq 0$ is a natural number representing the number of viruses in the system that belongs to strain $j \geq 0$.

Healthy agents of type 0 are those which have never encountered a virus, while viruses of strain 0 are those which have never come into contact with the anti-viral agent.

All the entities we consider enter the system at some specific rate, and diffuse through the system at specific rates. This corresponds, for instance, to the behaviour of entities which are suspended in a liquid.

Healthy agents of type i are added to the system (for instance via arrival into the system, or via agent division) at some rate λ_i ; they diffuse through the system at rate μ_i and are eliminated from the system (e.g. as a consequence of agent death or some other form of elimination) at rate $d_i\mu_i$ where d_i can be interpreted as a probability. Infected agents result only from the infection of healthy agents, i.e. we do not assume that infected agents enter the system from some outside source. The infected agents diffuse at rate μ , they die at rate $d\mu$, where d is a probability, and at rate $(1-d)\mu$ they leave the system before they die.

Viruses belonging to strain j enter the system at some rate β_j and diffuse at rate γ_j . They are eliminated naturally at rate $b_j\gamma_j$ where $0 \leq b_j \leq 1$ is a probability. Thus different virus strains may be more or less “durable”, just as certain types of agents may survive longer than others.

When an infected agent dies, we assume that it generates an additional virus of strain $j=0$. Infected agents could potentially generate a large number of viruses; however the mathematical model is restricted to this simpler case for the time being. Furthermore, the reduced virulence of infected agents could also be attributed to the presence of the anti-viral agent. Also we could imagine that the genetic strain of the viruses generated by an infected agent should somehow mimic the strain of the viruses that infected it. Thus in both of these respects, as in other aspects, our model is a mathematical simplification of a much more complex reality.

An anti-viral agent's units (e.g. molecules) enter the medium at rate α , and diffuse in the medium at rate δ . During diffusion, they are removed from the medium with probability $0 \leq f \leq 1$. With probability $(1-f)$ a unit of the anti-viral agent will bind with some virus. With probability w_j an anti-viral

agent molecule attaches itself to a virus of strain j so that $\sum_{j=0}^{\infty} w_j(1-f)$. If, on the other hand, there are no viruses of that strain available, the unit or molecule of the anti-viral agent will be wasted.² Once the anti-viral agent binds with its selected virus of type j , it will destroy it with probability r_j , or the virus will survive with probability $(1-r_j)$. If the virus survives, it is now viewed as being a virus of strain $j+1$.

Note that the diffusion rates express activity rates of the corresponding entities via their mobility or their natural ability to engage other entities. The rates will depend on the medium in the system (e.g. water, blood plasma), the size and mass of the agents, the obstacles they may encounter, their electrical properties or those of the medium or environment, and so on. In mathematical terms, these rates are the parameters of independent and identically distributed exponential random variables. Also, we model the external arrival processes of viruses, anti-viral agents and agents as mutually independent Poisson processes.

2.1. The encounter of agents and viruses

Infection of healthy agents occurs as a result of the encounter of healthy agents and viruses. As indicated earlier, once an agent is infected, it will die at some rate μd and as a result will produce a virus. We model the infection process as follows.

Viruses belonging to strain j , when they are not naturally eliminated from the system, will diffuse at rate γ_j , and will be eliminated from the system at rate $\gamma_j b_j$. Viruses of strain j will target agents of strain i with probability z_{ji} where $\sum_{i=0}^{\infty} z_{ji} = 1$. Thus the probability z_{ji} expresses the preference of the virus of strain j for an agent of type or strain i .

Similarly, a normal agent of type i will diffuse through the system at rate μ_i and be eliminated from the system before it encounters a virus with probability d_i . As it diffuses in the system, the agent will have preferentially bound with viruses of type j with probability y_{ij} , $\sum_{j=0}^{\infty} y_{ij} = 1$.

The healthy agent of type i that is involved in either of these encounters with a virus of type j will become infected with probability p_{ji} , or with probability $(1-p_{ji})$ it remains uninfected. If it does not become infected, it will now have become an agent of type $i+1$. This model can represent either a mutation of the agent into a more resistant (or simply different) strain as a result of the encounter with the virus, or it may represent the fact that the agent's strain is being revealed by the encounter with the virus.

The model can also represent situations where an agent's resistance changes in a non-monotone fashion (e.g. it becomes "stronger" and then "weaker") as a result of successive encounters with viruses. In other words p_{ji} may decrease as i increases, or it may increase with i , or it may remain unchanged, and there may be a decrease followed by an increase and so on.

² The model that has been formulated could potentially allow the design of an "optimal cocktail" of anti-viral agents, by choosing the best probability distribution w_j which in some sense minimises the infection and helps to increase the survival rate of agents.

2.2. Analogy with a network of queues

Queueing models (Kelly, 1978; Asmussen, 1987) are commonly used to represent traffic in computer and communication networks or to describe the workload in computer systems (Onvural, 1995; Gelenbe and Pujolle, 1998), and to analyse the performance of manufacturing systems or traffic on roads. Thus a significant body of literature on queueing networks exists and many relevant analytical techniques have been developed for their solution. It is therefore useful to consider the natural analogy that arises between the model we describe in this paper and a queueing network in which "customers" correspond to healthy or infected agents, viruses or molecules of anti-viral agent, and the queue length associated with any one of these entities is the instantaneous number of entities of each kind which are present in the system.

A significant difference is that queueing theory typically models customers which visit some service centre, then wait in line, receive service and then may move to some other service centre. In our case, customers combine with each other (for instance when a virus combines with a healthy agent to create an infected agent), or are allowed to destroy each other (as when a molecule of the anti-viral agent de-activates a virus). In this respect, the model considered in this paper is similar to a class of models we had introduced earlier (Gelenbe, 1993; Gelenbe and Fournneau, 2002) which include "negative customers" and "triggers" which allow certain customers to destroy others and also to force them to move to different service centres, but with yet another significant difference. Due to the need to represent a countably very large number of genetic differences between viruses and among agents, and because viruses and agents may mutate naturally or in response to external stimuli, the model introduced in this paper deals with countably infinite and interdependent birth-and-death processes, rather than a finite set of queues and service centres as is usual in queueing theory.

Thus the continuous time Markov chains we consider are defined over infinitely many states arising from the unbounded number of strains or types of agents and of viruses, the unbounded number of agents and viruses of each strain, the unbounded number of infected agents, and the unbounded quantity of anti-viral agent.

3. State equations of the model

The system can be described at time $t \geq 0$ by an infinite random vector:

$$X(t) = [I(t), a(t), C_0(t), \dots, C_i(t), \dots, V_0(t), \dots, V_j(t), \dots] \quad (1)$$

which represents the number of infected agents, the concentration of anti-viral agent, the number of healthy agents of each type, and the number of viruses of each strain. The total number of agents and viruses are given by

$$C(t) = \sum_{i=0}^{\infty} C_i(t) \quad (2)$$

$$V(t) = \sum_{j=0}^{\infty} V_j(t)$$

For notational convenience we denote by c_i the infinite vector that is zero everywhere except that it is +1 in the position corresponding to $C_i(t)$, while v_j is the infinite vector which is zero everywhere except for the value +1 in the position $V_j(t)$. Similarly, let e_i be the infinite vector which is zero everywhere except that it has a +1 in its first position and e_A be the infinite vector that is zero everywhere except for its second position that is +1.

Let $x = [\iota, a, C_0, \dots, C_i, \dots, V_0, \dots, V_j, \dots]$ be the deterministic vector which represents some specific value taken by $X(t)$. The quantity we will examine is the probability distribution $p(x, t) = \text{Prob}[X(t) = x | X(0) = x_0]$ for some appropriate initial condition x_0 .

From the system description provided in the previous section, we can write state transition equations over the very small time interval $[t, t + \Delta t]$ for $p(x, t)$ as follows:

$$p(x, t + \Delta t) = o(\Delta t) + \Delta t \{ p(x - e_A, t) \alpha 1[a > 0] + \sum_{i=0}^{\infty} p(x - c_i, t) \lambda_i 1[C_i > 0] \} \tag{3}$$

$$+ \sum_{j=0}^{\infty} p(x - v_j, t) \beta_j 1[V_j > 0] + p(x + e_A, t) \delta f + \sum_{i=0}^{\infty} p(x + c_i, t) d_i \mu_i \tag{4}$$

$$+ \sum_{j=0}^{\infty} p(x + v_j, t) b_j \gamma_j + p(x + e_i - v_0, t) \mu d 1[V_0 > 0] + p(x + e_i, t) \mu (1 - d)$$

$$+ \sum_{i,j=0}^{\infty} p(x + c_i - c_{i+1} + v_j, t) [\gamma_j z_{ji} + \mu_i y_{ij}] 1[C_{i+1} > 0] (1 - p_{ji})$$

$$+ \sum_{i,j=0}^{\infty} [p(x + v_j, t) \gamma_j z_{ji} 1[C_i = 0] + p(x + c_i, t) \mu_i y_{ij} 1[V_j = 0]]$$

$$+ \sum_{i,j=0}^{\infty} p(x - e_i + c_i + v_j, t) [\gamma_j z_{ji} + \mu_i (1 - d_i)] y_{ij} 1[\iota > 0] p_{ji}$$

$$+ \sum_{j=0}^{\infty} [p(x + e_A + v_j, t) \delta (1 - f) w_j r_j + p(x + e_A + v_j - v_{j+1}, t) \delta (1 - f) w_j (1 - r_j) 1[V_{j+1} > 0]]$$

$$+ \sum_{j=0}^{\infty} p(x + e_A, t) \delta (1 - f) w_j 1[V_j = 0] \}$$

$$- (1 - \alpha \Delta t) (1 - \delta \Delta t 1[a > 0]) (1 - \mu \Delta t 1[\iota > 0]) \prod_{i=0}^{\infty} [(1 - \lambda_i \Delta t) (1 - \mu_i 1[C_i > 0] \Delta t)] \dots$$

$$\dots \prod_{j=0}^{\infty} [(1 - \beta_j \Delta t) (1 - \gamma_j 1[V_j > 0] \Delta t)] p(x, t)$$

- Line 3: The first term concerns the probability of natural elimination from the system of viruses of each strain, the second term describes the event related to the death of an infected agent and the resulting release of a virus, while the third term covers the case where an infected agent is eliminated from the environment we consider.
- Line 4: Both terms cover the encounter of a healthy agent of type i with a virus of strain j when this *does not* result in the infection of the agent; as a consequence the agent's type becomes $i + 1$ and the virus is eliminated. Line 5 deals with the case where there are no agents of the specific strain that are targeted by the virus, or there are no viruses of the strain the agent can bind with.
- Line 6: In this case, an agent of type i encounters a virus of type j and infection does occur and the virus is incorporated into the infected agent.
- Line 7: A unit of the anti-viral agent encounters a virus of strain $j = 0, 1, \dots$, and either the virus is destroyed, or

where the explanation of the terms on the right-hand side is given line by line as follows:

- Line 1: the first term $o(\Delta t)$ covers all second order terms obtained by two or more simultaneous events, while the second term corresponds to external arrivals of anti-viral agent molecules into the medium, and the third term represents external arrivals of agents of type i into the medium.
- Line 2: The first term represents the probability of external arrivals of viruses of each strain, while the second and third terms represent the probabilities of natural elimination from the medium of molecules of the anti-viral agent and of healthy agents of each type, respectively.

the virus survives and mutates into a virus of one higher strain.

- Line 8: This covers the case where it so happens that a molecule of the anti-viral agent which diffuses through the system is targeting viruses of strain j , but at that instant there are no viruses of that strain in the system. Of course, we sum over all strains of viruses (over all j) so that all such possible cases are covered.
- The last two lines cover the probability that none of these events occurs.

By subtracting terms and dividing both sides by Δt we obtain:

$$\frac{p(x, t + \Delta t) - p(x, t)}{\Delta t} = \frac{o(\Delta t)}{\Delta t} + p(x - e_A, t)\alpha 1[a > 0] + \sum_{i=0}^{\infty} p(x - c_i, t)\lambda_i 1[C_i > 0] \quad (5)$$

$$+ \sum_{j=0}^{\infty} p(x - v_j, t)\beta_j 1[V_j > 0] + p(x + e_A, t)\delta f + \sum_{i=0}^{\infty} p(x + c_i, t)d_i \mu_i \quad (6)$$

$$+ \sum_{j=0}^{\infty} p(x + v_j, t)b_j \gamma_j + p(x + e_i - v_0, t)d\mu 1[V_0 > 0] + p(x + e_i, t)\mu(1 - d)$$

$$+ \sum_{i,j=0}^{\infty} p(x + c_i - c_{i+1} + v_j, t) [\gamma_j z_{ji} + \mu_i y_{ij}] 1[C_{i+1} > 0] (1 - p_{ji})$$

$$+ \sum_{i,j=0}^{\infty} [p(x + v_j, t) [\gamma_j z_{ji} 1[C_i = 0] + p(x + c_i, t)\mu_i y_{ij} 1[V_j = 0]]$$

$$+ \sum_{i,j=0}^{\infty} p(x - e_i + c_i + v_j, t) [\gamma_j z_{ji} + \mu_i(1 - d_i)] y_{ij} 1[l > 0] p_{ji}$$

$$+ \sum_{j=0}^{\infty} [p(x + e_A + v_j, t)\delta(1 - f)w_j r_j + p(x + e_A + v_j - v_{j+1}, t)\delta(1 - f)w_j(1 - r_j) 1[V_{j+1} > 0]]$$

$$+ \sum_{j=0}^{\infty} p(x + e_A, t)\delta(1 - f)w_j 1[V_j = 0]$$

$$- \left\{ \alpha + \delta + \mu 1[l > 0] + \sum_{i=0}^{\infty} [\lambda_i + \mu_i 1[C_i > 0]] + \sum_{j=0}^{\infty} [\beta_j + \gamma_j 1[V_j > 0]] \right\} p(x, t)$$

Now taking the limit as $\Delta t \rightarrow 0$, and then using the fact that $\lim_{\Delta t \rightarrow 0} o(\Delta t)/\Delta t = 0$, we obtain the Chapman-Kolmogorov or backwards equation (6) for the system under consideration:

$$\frac{dp(x, t)}{dt} = p(x - e_A, t)\alpha 1[a > 0] + \sum_{i=0}^{\infty} p(x - c_i, t)\lambda_i 1[C_i > 0] \quad (7)$$

$$+ \sum_{j=0}^{\infty} p(x - v_j, t)\beta_j 1[V_j > 0] + p(x + e_A, t)\delta f + \sum_{i=0}^{\infty} p(x + c_i, t)d_i \mu_i \quad (8)$$

$$+ \sum_{j=0}^{\infty} p(x + v_j, t)b_j \gamma_j + p(x + e_i - v_0, t)d\mu 1[V_0 > 0] + p(x + e_i, t)\mu(1 - d)$$

$$+ \sum_{i,j=0}^{\infty} p(x + c_i - c_{i+1} + v_j, t) [\gamma_j z_{ji} + \mu_i y_{ij}] 1[C_{i+1} > 0] (1 - p_{ji}) \quad (9)$$

$$+ \sum_{i,j=0}^{\infty} [p(x + v_j, t) [\gamma_j z_{ji} 1[C_i = 0] + p(x + c_i, t)\mu_i y_{ij} 1[V_j = 0]] \quad (10)$$

$$+ \sum_{i,j=0}^{\infty} p(x - e_i + c_i + v_j, t) [\gamma_j z_{ji} + \mu_i(1 - d_i)] y_{ij} 1[l > 0] p_{ji}$$

$$+ \sum_{j=0}^{\infty} [p(x + e_A + v_j, t)\delta(1 - f)w_j r_j + p(x + e_A + v_j - v_{j+1}, t)\delta(1 - f)w_j(1 - r_j) 1[V_{j+1} > 0]] \quad (11)$$

$$+ \sum_{j=0}^{\infty} p(x + e_A, t)\delta(1 - f)w_j 1[V_j = 0] \quad (12)$$

$$- \left\{ \alpha + \delta 1[a > 0] + \mu 1[l > 0] + \sum_{i=0}^{\infty} [\lambda_i + \mu_i 1[C_i > 0]]$$

$$+ \sum_{j=0}^{\infty} [\beta_j + \gamma_j 1[V_j > 0]] \right\} p(x, t)$$

If the stationary solution $p(x)$ given by $p(x) = \lim_{t \rightarrow +\infty} p(x, t)$ exists, then it is known (6) that it must satisfy the backwards equation (8) with $(d/dt)p(x, t) = 0$. In the sequel we will concern ourselves with the computation of the stationary solution which gives the general equilibrium between the different populations we are considering.

4. Stationary solution

From the infinite system of differential-difference equations given above, it is difficult to deduce the dynamics of the

$$\quad (7)$$

$$\quad (8)$$

$$\quad (9)$$

$$\quad (10)$$

$$\quad (11)$$

$$\quad (12)$$

system. However, the stationary solution of these equations provides significant insight into the equilibria which are established between different entities. Let us define the following quantities:

$$A_{ji}^- = q_j \gamma_j z_{ji}, \quad i, j \geq 0 \quad (13)$$

$$A_i = \sum_{j=0}^{\infty} A_{ji}^-, \quad i \geq 0 \quad (14)$$

$$\lambda_{ij}^- = \rho_i \mu_i \gamma_{ij}, \quad i, j \geq 0 \quad (15)$$

$$\lambda_{Aj}^- = q_A \delta w_j, \quad j \geq 0 \quad (16)$$

$$A_i^+ = \lambda_i + \sum_{j=0}^{\infty} [A_{j,i-1}^- \rho_{i-1} + \lambda_{i-1,j}^- q_j] (1 - p_{j,i-1}), \quad i \geq 1 \quad (17)$$

$$F_j^- = \lambda_{Aj}^- + \sum_{i=0}^{\infty} \lambda_{ij}^-, \quad j \geq 0 \quad (18)$$

$$F_j^+ = \beta_j + \lambda_{Aj-1}^- q_{j-1} (1 - r_{j-1}), \quad j \geq 1 \quad (19)$$

The expressions (14)–(19) can be interpreted as follows:

- The total rate at which viruses which diffuse in the system interact with healthy agents of type i , either resulting in an infected agent or in a healthy agent of type $i + 1$, in effect reducing each time the number of healthy agents by 1.
- The total rate at which healthy agents of type i join the system either from external sources or by mutation of an agent of type $i - 1$ which survives an encounter with a virus.
- The total rate at which viruses of type j are removed either because they are destroyed by the anti-viral agent or because a healthy agent that is diffusing through the system encounters the virus, becomes infected and incorporates the virus, or does not become infected and eliminates the virus.
- Finally, the total rate at which viruses of type $j \geq 1$ are replenished, either through external arrivals or by mutation after an encounter with the anti-viral agent does not result in the destruction of a virus of strain $j - 1$.

Now let

$$q_A = \frac{\alpha}{\delta} \quad (20)$$

$$\rho_0 = \frac{\lambda_0}{\mu_0 + A_0} \quad (21)$$

$$\rho_i = \frac{A_i^+}{\mu_i + A_i}, \quad i \geq 1 \quad (22)$$

$$q_0 = \frac{\beta_0 + q_I \mu d}{\gamma_0 + F_0^-} \quad (23)$$

$$q_j = \frac{F_j^+}{\gamma_j + F_j^-}, \quad j \geq 1 \quad (23)$$

$$q_I = \frac{\sum_{i,j=0}^{\infty} [A_{j,i}^- \rho_i + \lambda_{ij}^- q_j] p_{ji}}{\mu} \quad (24)$$

Because we are dealing with an infinite vector x , in order to avoid having zero values of the probability associated with each infinite vector, we will express the results in terms of the

marginal probabilities over any finite sub-vector $x_{n,m} = [l, a, C_0, \dots, C_n, V_0, \dots, V_m]$ where we only consider the first n strains of cells, and m strains of viruses. Of course, n, m can be chosen arbitrarily so the result maintains its full generality. We then have:

$$p(x_{n,m}, t) = \sum_{i=n+1}^{\infty} \sum_{j=m+1}^{\infty} p(x, t) \quad (25)$$

and $p(x_{n,m}) = \lim_{t \rightarrow +\infty} p(x_{n,m}, t)$

Theorem. The stationary solution to the system of equations (8) for any $n, m \geq 0$ is given by

$$p(x_{n,m}) = G_{n,m} q_A^a q_I^l \left[\prod_{i=0}^n (\rho_i)^{C_i} \right] \left[\prod_{j=0}^m (q_j)^{V_j} \right] \quad (26)$$

provided that $0 \leq q_A, q_I, \rho_i, q_j < 1$, for all $i, j = 0, \dots, \infty$, where $G_{n,m} = (1 - q_A)(1 - q_I) \prod_{i=0}^n (1 - \rho_i) \prod_{j=0}^m (1 - q_j)$ is a normalising constant.

The proof of the theorem is provided in Appendix 1.

Furthermore, it is easy to see that in steady state, the average number:

- of infected agents is given by $q_I [1 - q_I]^{-1}$, if $q_I < 1$,
- of healthy agents of strain i is given by $\rho_i [1 - \rho_i]^{-1}$, if $\rho_i < 1$,
- and of viruses of strain j is given by $q_j [1 - q_j]^{-1}$, if $q_j < 1$.

5. A simple consequence and a heuristic rule

The purpose of using the anti-viral agent is to avoid the explosive growth of the number of infected agents and viruses. Thus we are interested in finding how we can most effectively use the anti-viral agent to keep these numbers under control, or to drive them to zero.

The i th strain of healthy agents is those which remains healthy after i encounters with a virus. Thus we can take $\lambda_i = 0$ for $i \geq 1$ so that all new or untested agents are considered to be of strain 0. Similarly, we assume that a virus' strain is only revealed by its successive survivals to encounters with the anti-viral agent, so that $\beta_j = 0$ for $j \geq 1$. With these assumptions the expressions (21)–(24) yield:

$$q_I = \frac{\sum_{i,j=0}^{\infty} \rho_i q_j [\gamma_j z_{ji} + \mu_i \gamma_{ij}] p_{ji}}{\mu} \quad (27)$$

so that for $j \geq 1$,

$$q_j = \frac{\lambda_{Aj-1}^- q_{j-1} (1 - r_{j-1})}{\gamma_j + q_A \delta w_j + \sum_{i=0}^{\infty} \rho_i \mu_i \gamma_{ij}} \quad (28)$$

$$= q_0 P(j) \quad (29)$$

$$P(j) = \alpha^j \prod_{l=1}^j \frac{w_{l-1} (1 - r_{l-1})}{\gamma_l + \alpha w_l + \sum_{i=0}^{\infty} \rho_i \mu_i \gamma_{il}} \quad (30)$$

while for $i \geq 1$,

$$\rho_i = \rho_{i-1} \frac{\sum_{j=0}^{\infty} q_j [\gamma_j z_{j,i-1} + \mu_i y_{i-1,j}] (1 - p_{j,i-1})}{\mu_i + \sum_{j=0}^{\infty} q_j \gamma_j z_{ji}} \quad (31)$$

$$= \rho_0 \prod_{l=1}^i \frac{\sum_{j=0}^{\infty} q_j [\gamma_j z_{j,l-1} + \mu_l y_{l-1,j}] (1 - p_{j,l-1})}{\mu_l + \sum_{j=0}^{\infty} q_j \gamma_j z_{jl}} \quad (32)$$

and

$$q_0 = \frac{\beta_0 + \sum_{i,j=0}^{\infty} \rho_i q_j [\gamma_j z_{ji} + \mu_i y_{ij}] p_{ji}}{\gamma_0 + \alpha w_0 + \sum_{i=0}^{\infty} \rho_i m y_{i0}} \quad (33)$$

$$= \frac{\beta_0}{\gamma_0 + \alpha w_0 + \sum_{i=0}^{\infty} \rho_i \mu_i y_{i0} - q_0 \sum_{i,j=0}^{\infty} \rho_i P(j) [\gamma_j z_{ji} + \mu_i y_{ij}] p_{ji}} \quad (34)$$

$$\rho_0 = \frac{\lambda_0}{\mu_0 + \sum_{j=0}^{\infty} q_j \gamma_j z_{j0}} \quad (35)$$

Let us now see how (30) can provide us with insight about the use of the anti-viral agent. Let us express a heuristic rule, and then show how it is justified using the results we have presented.

A *heuristic rule*: First of all, notice from (34) that if we can choose αw_0 to be arbitrarily large, then we can set q_0 to a value less than 1, and in fact set it to as small a value as we wish. Obviously, there will be natural limits to this since at some level of concentration, the anti-viral agent will impair the normal behaviour of uninfected agents. Once a small enough value of q_0 has been achieved using a large enough value of αw_0 , we turn to (30) and see intuitively that we must also insure that $P(j)$ does not grow as j increases. An obvious way of doing this is to set $w_j > w_{j-1}(1 - r_{j-1})$, in other words the fraction of anti-viral agent which is devoted to controlling the j th viral strain should be larger than the fraction allotted to the $j - 1$ th strain multiplied by the probability that viruses of the $j - 1$ th strain survive an encounter with the anti-viral agent.

Let us now put this recommendation on a more rigorous mathematical footing. Assume first that have been able to achieve $q_0 < 1$. Then if all the $P(j) < 1$ we are sure that the $q_j < 1$ for $j \geq 1$. However, this does not suffice to guarantee that the size of the virus population is under control, i.e. that in steady state the average size of the virus population remains finite:

$$V = \sum_{j=0}^{\infty} \frac{q_j}{1 - q_j} < +\infty \quad (36)$$

However, we can show that if $q_0 < 1$ and $w_j \geq w_{j-1}(1 - r_{j-1})$ so that all $q_j < 1$, then $V < +\infty$ provided that

$$\lim_{j \rightarrow +\infty} \frac{w_j(1 - r_j)}{w_{j+1}} = 0 \quad (37)$$

Indeed, if $q_j < 1$ for $j \geq 0$, then

$$V = \sum_{j=0}^{\infty} \frac{q_j}{1 - q_j} \leq \sum_{j=0}^{\infty} [q_j + q_j^3] \quad (38)$$

Since each $0 \leq q_j < 1$, it follows that $\sum_{j=0}^{\infty} q_j^3 < +\infty$ whenever $\sum_{j=0}^{\infty} q_j < +\infty$, and the latter series converges if $\lim_{j \rightarrow +\infty} q_j / q_{j-1} = 0$, hence the claim.

Since the expressions obtained in the steady-state solution are non-linear, in general we should determine the existence and uniqueness of solutions to the equations we are dealing with. However, as a result of the parameter values being

selected, we have $q_j < 1$ for all $j \geq 0$, we are assured in this case of existence and uniqueness of the steady-state solution.

6. Conclusions

In this work, we suggest a probability model for populations of agents and viruses that interact in the presence of an anti-viral agent. Both agents and viruses can belong to different strains, and these strains are revealed as the agents, viruses and the anti-viral agent interact. Viruses that survive the effect of the anti-viral agent are considered to belong to a different strain from the one they started in, and their ability to survive a future encounter with molecules of the anti-viral agent is modified, as is their ability to infect a healthy agent. Similarly, agents which remain healthy after an encounter with a virus will now be identified as belonging to a new strain or type, and this will impact their future behaviour. Additionally, we assume that the anti-viral agent can be made up of a mix or cocktail, with different proportions of agents that target different strains of the virus.

We derive the state equations for the dynamics of the model in terms of the probability distribution of each possible state as a function of time, and show that in steady state these equations have a compact analytical solution. This solution is used to provide insight into the appropriate mix or ‘‘cocktail’’ of anti-viral agent that is needed to keep the infection under control. One insight that the model provides is that the concentration of anti-viral agent by itself does not suffice to ultimately control the infection, and that it is important to distribute the effectiveness of the anti-viral agent over all strains of the virus in a specific manner, taking into account both the overall dosage mechanism and the ability of each virus strain to survive. We hope that such results may eventually help to develop improved therapeutic protocols based on computer aided design methods.

This model can benefit from many extensions that would allow a better understanding of the interaction of agents and viruses, or of agents and other infectious agents, in the presence of naturally produced or synthetically introduced chemical agents. We could, for instance, consider a mutation mechanism for agents and viruses which is independent of the interaction between all these elements. We could also study the noxious effects of the anti-viral agent on the healthy agents. It would also be very useful to model protocols which include anti-viral treatment together with techniques that improve the immunity of healthy agents, and also to model techniques that render infected agents incapable of producing viral material. We conclude that this paper can stimulate research about some of these issues. Another direction of useful research would be to use the analytical results we have obtained to develop algorithms for the optimisation of therapeutic strategies.

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Appendix 1.

The proof of **Theorem 1** is by direct substitution of (26) into Eq. (8) when we set $dp(x, t)/dt = 0$ and replace $p(x, t)$ by $p(x)$. Carrying out this substitution, moving the last term in (8) to the left-hand-side, and dividing both sides of the system of equations by the value of $p(x)$ given in (26) we get

$$\begin{aligned} & \alpha + \delta 1[a > 0] + \mu 1[\iota > 0] + \sum_{i=0}^{\infty} [\lambda_i + \mu_i 1[C_i > 0]] \\ & + \sum_{j=0}^{\infty} [\beta_j + \gamma_j 1[V_j > 0]] = \frac{\alpha 1[a > 0]}{q_A} + \sum_{i=0}^{\infty} \frac{\lambda_i 1[C_i > 0]}{\rho_i} \\ & + \sum_{j=0}^{\infty} \frac{\beta_j 1[V_j > 0]}{q_j} + q_A \delta f + \sum_{i=0}^{\infty} \rho_i d_i \mu_i + \sum_{j=0}^{\infty} q_j b_j \gamma_j + \frac{q_1 d \mu 1[v_0 > 0]}{Q_0} \\ & + q_1 (1-d) \mu + \sum_{i,j=0}^{\infty} \frac{\rho_i q_j}{\rho_{i+1}} [\gamma_j z_{ji} + \mu_i y_{ij}] 1[C_{i+1} > 0] (1-p_{ji}) \\ & + \sum_{i,j=0}^{\infty} \frac{\rho_i q_j}{q_i} [\gamma_j z_{ji} + \mu_i y_{ij}] p_{ji} 1[\iota > 0] + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j \\ & + \sum_{j=0}^{\infty} \frac{q_A q_j}{q_{j+1}} \delta \omega_j (1-r_j) 1[V_{j+1} > 0] + \sum_{i,j=0}^{\infty} [q_j \gamma_j z_{ji} 1[C_i = 0] \\ & + \rho_i \mu_i y_{ij} 1[V_j = 0]] + \sum_{j=0}^{\infty} q_A \delta \omega_j 1[V_j = 0] \end{aligned} \quad (39)$$

which, after simplification, yields

$$\begin{aligned} & \alpha + \sum_{i=0}^{\infty} [\lambda_i + \mu_i 1[C_i > 0]] + \sum_{j=0}^{\infty} [\beta_j + \gamma_j 1[V_j > 0]] \\ & = \sum_{i=0}^{\infty} \frac{\lambda_i 1[C_i > 0]}{\rho_i} + \sum_{j=0}^{\infty} \frac{\beta_j 1[V_j > 0]}{q_j} + q_A \delta f + \sum_{i=0}^{\infty} \rho_i d_i \mu_i \\ & + \sum_{j=0}^{\infty} q_j b_j \gamma_j + \frac{q_1 d \mu 1[V_0 > 0]}{q_0} + q_1 (1-d) \mu \\ & + \sum_{i=0}^{\infty} \frac{A_{i+1}^+ - \lambda_{i+1}}{\rho_{i+1}} 1[C_{i+1} > 0] + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j \\ & + \sum_{j=0}^{\infty} \frac{F_{j+1}^+ - \beta_{j+1}}{q_{j+1}} 1[V_{j+1} > 0] + \sum_{i=0}^{\infty} A_i 1[C_i = 0] + \sum_{i=0}^{\infty} F_j^- 1[V_j = 0] \\ & = [\mu_0 + A_0] 1[C_0 > 0] + [\gamma_0 + F_0^-] 1[V_0 > 0] + q_A \delta f + \sum_{i=0}^{\infty} \rho_i d_i \mu_i \\ & + \sum_{j=0}^{\infty} q_j b_j \gamma_j + q_1 (1-d) \mu + \sum_{i=1}^{\infty} A_i 1[C_i > 0] + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j \\ & + \sum_{j=1}^{\infty} F_j^- 1[V_j > 0] + \sum_{i=0}^{\infty} A_i 1[C_i = 0] + \sum_{j=0}^{\infty} F_j^- 1[V_j = 0] \end{aligned} \quad (40)$$

or

$$\begin{aligned} & \alpha + \sum_{i=0}^{\infty} \lambda_i + \sum_{j=0}^{\infty} \beta_j = q_A \delta f + \sum_{i=0}^{\infty} \rho_i d_i \mu_i + \sum_{j=0}^{\infty} q_j b_j \gamma_j + q_1 (1-d) \mu \\ & + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j + \sum_{j=0}^{\infty} F_j^- + \sum_{i=0}^{\infty} A_i \end{aligned} \quad (41)$$

Now note that

$$\begin{aligned} & \rho_i \mu_i d_i = \rho_i \mu_i - \sum_{j=0}^{\infty} \rho_i \mu_i y_{ij} \\ & = \lambda_0 - A_0 \rho_0 - \sum_{j=0}^{\infty} \rho_0 \mu_0 y_{0j}, \quad \text{for } i = 0 \\ & = A_i^+ - A_i \rho_i - \sum_{j=0}^{\infty} \rho_i \mu_i y_{ij}, \quad \text{for } i \geq 1 \end{aligned} \quad (42)$$

and

$$\begin{aligned} & q_j \gamma_j b_j = q_j \gamma_j - \sum_{i=0}^{\infty} q_j \gamma_j z_{ji} \\ & = \beta_0 - q_1 \mu d - \sum_{i=0}^{\infty} q_0 \gamma_0 z_{0i}, \quad \text{for } j = 0 \\ & = F_j^+ - F_j^- q_j - \sum_{i=0}^{\infty} q_j \gamma_j z_{ji}, \quad \text{for } j > 0 \end{aligned} \quad (43)$$

so that

$$\begin{aligned} & \sum_{i=0}^{\infty} \rho_i \mu_i d_i + \sum_{j=0}^{\infty} q_j \gamma_j b_j = \sum_{i=1}^{\infty} (A_i^+ - A_i \rho_i) + \lambda_0 - A_0 \rho_0 \\ & + \sum_{j=1}^{\infty} (F_j^+ - F_j^- q_j) + \beta_0 + q_1 \mu d - F_0^- q_0 \\ & - \sum_{i,j=0}^{\infty} \rho_i \mu_i y_{ij} - \sum_{i,j=0}^{\infty} q_j \gamma_j z_{ji} \end{aligned} \quad (44)$$

Thus (41) reduces to

$$\begin{aligned} & \alpha + \sum_{i=0}^{\infty} \lambda_i + \sum_{j=0}^{\infty} \beta_j = q_A \delta - \sum_{i=0}^{\infty} q_A \delta \omega_j + \sum_{i=1}^{\infty} (A_i^+ - A_i \rho_i) \\ & + \lambda_0 - A_0 \rho_0 + \sum_{j=1}^{\infty} (F_j^+ - F_j^- q_j) + \beta_0 + q_1 \mu d - F_0^- q_0 \\ & + q_1 (1-d) \mu + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j + \sum_{j=0}^{\infty} F_j^- + \sum_{i=0}^{\infty} A_i \\ & - \sum_{i,j=0}^{\infty} [\rho_i \mu_i y_{ij} + q_j \gamma_j z_{ji}] \end{aligned} \quad (45)$$

or

$$\begin{aligned} & 0 = q_1 \mu - \sum_{j=0}^{\infty} q_A \delta \omega_j + \sum_{i,j=0}^{\infty} [A_{j,i}^- \rho_i + \lambda_{i,j} q_j] (1-p_{j,i}) - \sum_{i=0}^{\infty} A_i \rho_i \\ & - \sum_{i,j=0}^{\infty} [\rho_i \mu_i y_{ij} + q_j \gamma_j z_{ji}] + \sum_{j=0}^{\infty} \lambda_{A,j} q_j (1-r_j) - \sum_{j=0}^{\infty} F_j^- q_j \\ & + \sum_{j=0}^{\infty} q_A q_j \delta \omega_j r_j + \sum_{j=0}^{\infty} F_j^- + \sum_{i=0}^{\infty} A_i \\ & = - \sum_{j=0}^{\infty} q_A \delta \omega_j + \sum_{i,j=0}^{\infty} [A_{j,i}^- \rho_i + \lambda_{i,j} q_j] - \sum_{i=0}^{\infty} A_i \rho_i + \sum_{j=0}^{\infty} \lambda_{A,j} q_j \\ & - \sum_{i,j=0}^{\infty} [\rho_i \mu_i y_{ij} + q_j \gamma_j z_{ji}] - \sum_{j=0}^{\infty} F_j^- q_j + \sum_{j=0}^{\infty} F_j^- + \sum_{i=0}^{\infty} A_i \\ & = - \sum_{j=0}^{\infty} q_A \delta \omega_j + \sum_{i,j=0}^{\infty} [A_{j,i}^- \rho_i + \lambda_{i,j} q_j] - \sum_{i=0}^{\infty} A_i \rho_i + \sum_{j=0}^{\infty} \lambda_{A,j} q_j \\ & - \sum_{i,j=0}^{\infty} [\rho_i \mu_i y_{ij} + q_j \gamma_j z_{ji}] - \sum_{j=0}^{\infty} \lambda_{A,j} q_j - \sum_{i,j=0}^{\infty} \lambda_{i,j} q_j + \sum_{j=0}^{\infty} \lambda_{A,j} q_j \\ & + \sum_{i,j=0}^{\infty} \lambda_{i,j}^- + \sum_{i,j=0}^{\infty} q_j \gamma_j z_{ji} \end{aligned} \quad (46)$$

and we see that all terms on the right-hand-side cancel out, completing the proof of **Theorem 1**. \square

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