World Applied Sciences Journal 2 (2): 081-089, 2007
ISSN 1818-4952

Analysis and Approximation for Solving Highly Coupled Master Differential Equations of Receptor Interactions

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Abstract: Humoral immunity is one component of the human immune system and is the most important determinant of whether an invading pathogen (such as bacteria or viruses) establishes infection. This form of immunity is mediated by B lymphocytes and involves the neutralizing of pathogen receptor binding sites to inhibit the pathogen's entry into target cells. A master equation in both discrete and in continuous form is presented for a pathogen bound at n sites becoming a pathogen bound at m sites in a given interaction time. To track the time-evolution of the antibody-receptor interaction, it is shown that the process is most easily treated classically and that in this case the master equation can be reduced to an equivalent one-dimensional diffusion equation. Thus, well known diffusion theory can be applied to antibody-cell receptor interactions. Three distinct cases are considered depending on whether the probability of antibody binding compared to the probability of dissociation is relatively large, small or comparable and numerical solutions are given.

Key words: Receptor Interactions . Humoral immunity . Diffusion equation

INTRODUCTION

Antibodies bind to and block receptors on invading pathogens (such as viruses) and this reduces the pathogen's ability to attach to target cell receptors. As a consequence, the ability of the pathogen to enter a target cell is inhibited. In addition, antigen-bound antibodies produce a signal that activates specific white blood cells, the macrophages, which then engulf and destroy the bound pathogen. Since viruses and many bacteria reproduce within cells, blocking the cell attachment would limit such pathogens from replicating. The time-dependent dissociation and recombination of complexes formed by antibodies attaching to the surface of pathogens is a fundamental process in mathematical immunology, in general and in the study of humoral immunity, in particular and is the topic of investigation in this paper. The aim here is to provide a novel way of estimating the time-evolution of the distribution of the specific number of bound antibodies (aggregates of a certain size).

Two approaches have been used to calculate the aggregate size distribution. The first approach, the obvious one, is to write down differential equations in the form of chemical rate equations for the concentrations of all possible ligand-receptor aggregates [1] (ligands are cell surfaces with binding sites that may be bound). However, a complete description requires the solution of a large set of coupled ordinary differential equations [2], one for each aggregate. While this system is straightforward to formulate, the order of the system is very large. For example, rat basophilic leukemia cells have approximately 10^5 receptors per cell and a chlamydial elementary body has approximately 3×10^4 receptors. If this approach is used to estimate a time-dependent aggregate distribution size the set of equations must be truncated [1, 3]. A second approach is less general, but can be used to obtain the complete time-dependent aggregate size distribution by solving just two coupled nonlinear differential equations [4]. The kinetics of the ligand-receptor complexes distribution is presented in the form of a series [5, 6]. Although this works well for relatively small numbers of binding sites (1-100), a simpler mathematical approximation would be very useful for a system when the number of binding sites is significantly greater [7]. Here, another approach is developed to obtain the complete time-dependent aggregate size distribution for cell surfaces with many receptors (multivalent ligands) bound by molecules that bind at one receptor only. It involves solving a single diffusion equation. A single diffusion equation to describe the aggregate size distribution will be derived according to two methodologies. One example of such a binding molecule is the Fab fragment of an antibody. It comprises one arm of the full Y-shaped antibody. While this restricts the model's applicability to antibody-pathogen interactions in general, there are many systems for which this assumption is appropriate. For example, the pent-valent adenovirus requires full

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occupancy by antibodies to achieve neutralization. This can be achieved by Fabs but not whole antibodies (IgG molecules in this case) [8]. A similar phenomenon has been found in antibody-Chlamydia interactions [9]. It is also assume that all binding sites are equivalent and that adsorbed particles do not interact, that is, the binding of a molecule at one site does not block the binding at a neighbouring site.

Master equation of antibody attachment on an infectious particle: Consider an infectious particle bound at n sites by antibodies. Given that there is a probabilistically inferred rate at which the particle bound at n sites can become a particle bound at m sites, a well-known discrete version of any such model is of the form:

$$\frac{\partial E(n,t)}{\partial t} = \sum_{k=0}^{N}\left[K(m,n)E(m,t) - K(n,m)E(n,t)\right] \quad (1)$$

where, E(n, t) is the concentration of pathogens with n antibodies attached and N is the maximum number of antibodies that can be bound to a pathogen simultaneously. This equation states that particles bound by n antibodies may leave this state by making transitions to particles bound by m antibodies, gaining or losing antibodies, at a rate K(n, m)E(n, t); K(n, m) denotes the rate that particles bound at n sites become particles bound at m sites. Transitions from n antibodies to n-1 or n+1 (or remaining with n) antibodies on a particle can be expected to dominate the rate function, K.

The discrete Eq. (1) for the dynamics of the particle-antibody concentrations has the analogous continuous version,

$$\frac{\partial E(x,t)}{\partial t} = \int_0^f k(x', x)E(x', t) - k(x,x')E(x,t)dx' \quad (2)$$

where, k(x, x′) is the probabilistically inferred rate of undergoing a transition from state x to state x′ per unit time and f is the maximum number of antibodies on average that can attach to the surface of the pathogen simultaneously.

In the absence of immune clearance and cell infection the pathogen-antibody concentrations, E(x, t), have a non-trivial equilibrium distribution, which we denote by $E_e(x)$. At equilibrium,

$$\frac{\partial E(x,t)}{\partial t} = 0$$

and the requirement for detailed balancing [10] leads to the condition

$$R(x', x) = k(x',x)E_e(x') = k(x,x')E_e(x) = R(x,x') \quad (3)$$

From Eq. (3), we obtain

$$E_e(x') = \frac{P(x,x')}{P(x',x)}E_e(x) \quad (4)$$

Integrating both sides of Eq. (4) over the interval x′ = (0, f) and noting that because neither any source nor loss are considered, the number of pathogens will remain at a fixed level,

$$\int_0^f E_e(x')dx = E_0$$

then the following equilibrium distribution is obtained:

$$E_e(x) = E_0\left[\int_0^f \frac{P(x,x')}{P(x',x)}dx'\right]^{-1} \tag{5}$$

The equilibrium distribution is now used to introduce the non-dimensionalized concentration

$$X(x,t) = \frac{E(x,t)}{E_e(x)} \tag{6}$$

which is the ratio of the concentration of pathogens with x antibodies attached to the associated equilibrium concentration. Then, Eq. (2) can be written in the symmetrical form

$$E_e(x)\frac{\partial X(x,t)}{\partial t} = \int_0^f R(x,x')\left[X(x',t) - X(x,t)\right]dx' \tag{7}$$

Transformation to a diffusion equation by Taylor expansion of integrand: I now transform the master equation, Eq. (7), to an equivalent diffusion equation. The transformation assumes the integrand in Eq. (7) can be expanded in a Taylor series about $x' = x$ and I assume that the kernel, $R(x, x')$, is separable and large only for $x' \approx x$. I can then anticipate that the solution of Eq. (7) can be well approximated by the solution of

$$E_e(x)\frac{\partial X(x,t)}{\partial t} = \int_{-\infty}^{\infty} R(x,x')\left[X(x',t) - X(x,t)\right]dx' \tag{8}$$

$$E_e(x)\frac{\partial X}{\partial t} = \mu_1(x)\frac{\partial X}{\partial x} + \frac{\mu_2(x)}{2}\frac{\partial^2 X}{\partial x^2} + O(\mu_3) \tag{9}$$

where,

$$\mu_n(x) = \int_{-\infty}^{\infty} R(x,x')(x'-x)^n dx' \tag{10}$$

is the nth moment of the change in antibody level $(x'-x)$ with respect to $R(x, x')$. Observing symmetry of $R(x, x')$ on interchange of x and x' requires that

$$R(x,x') = S(\bar{x},|\Delta|) \tag{11}$$

where,

$$\bar{x} = (x'+x)/2 \tag{12}$$

is the mean of the initial and final antibody levels and

$$\Delta = x'-x \tag{13}$$

is the change in the antibody levels. Assuming $S(\bar{x},|\Delta|)$ is sharply peaked at $\Delta = 0$ I expand about $\Delta = 0$ and obtain

$$\mu_1(x) = \int_0^{\infty} \left.\frac{\partial S}{\partial \bar{x}}\right|_{\bar{x}=x} \Delta^2 d\Delta + O(\Delta^4) \tag{14}$$

and

$$\mu_2(x) = 2\int_0^{\infty} S(x,|\Delta|)\,\Delta^2 d\Delta + O(\Delta^4) \tag{15}$$

so that

$$\mu_1(x) = \frac{1}{2}\frac{\partial \mu_2}{\partial x} + O(\Delta^4) \tag{16}$$

and substituting (16) into (9) results in

$$E_e(x)\frac{\partial X}{\partial t} = \frac{\partial}{\partial x}\left(\frac{\mu_2(x)}{2}\frac{\partial X}{\partial x}\right) \tag{17}$$

a one-dimensional diffusion equation. The boundary conditions necessary to determine X(x,t) uniquely are

$$\left.\frac{\partial X}{\partial x}\right|_{x=0} = 0 \text{ and } \left.\frac{\partial X}{\partial x}\right|_{x=f} = 0 \tag{18}$$

since a pathogen cannot have a negative number of antibodies and will not have more than the maximum of f antibodies. Eq. (17) can be written as:

$$E_e(x)\frac{\partial X}{\partial t} = \frac{\mu_2(x)}{2}\frac{\partial^2 X}{\partial x^2} + \frac{1}{2}\frac{\partial \mu_2}{\partial x}\frac{\partial X}{\partial x} \tag{19}$$

and thus there are two components indicating how the distribution will change with time, namely, X will diffuse in the direction of least antibodies and will be balanced by what equilibrium should be according to the probability distribution that influences the moment, $\mu_2(x)$.

Transformation to a diffusion equation by assuming separable kernel: The second method of transforming (7) into a diffusion equation involves the assumption that the kernel, R(x, x′), can be separated in the form

$$R(x,x') = \begin{cases} r_1(x)\,r_2(x'), x' > x \\ r_1(x')\,r_1(x), x' < x \end{cases} \tag{20}$$

Substituting (20) into (7) I obtain

$$E_e(x)\frac{\partial X}{\partial t} + A(x)X(x,t) = r_2(x)\int_0^x r_1(x')X(x',t)\,dx' + r_1(x)\int_x^f r_2(x')X(x',t)\,dx' \tag{21}$$

where,

$$A(x) = r_2(x)\int_0^x r_1(x')\,dx' + r_1(x)\int_x^f r_2(x')\,dx' \tag{22}$$

On differentiating Eq. (21) twice with respect to x, I obtain

$$\frac{\partial}{\partial x}\left(E_e\frac{\partial X}{\partial t} + AX\right) = \frac{dr_2}{dx}\int_0^x r_1(x')X(x',t)\,dx' + \frac{dr_1}{dx}\int_x^f r_2(x')X(x',t)\,dx' \tag{23}$$

and

$$\frac{\partial^2}{\partial x^2}\left(E_e\frac{\partial X}{\partial t}+AX\right)=\frac{d^2r_2}{dx^2}\int_0^x r_1(x')X(x',t)dx'+\frac{d^2r_1}{dx^2}\int_x^f r_2(x')X(x',t)dx'-W\{r_2,r_1\}X(x,t) \tag{24}$$

where,

$$W\{r_2,r_1\}=r_2\frac{dr_1}{dx}-r_1\frac{dr_2}{dx} \tag{25}$$

is the Wronskian of r_2 and r_1. Combining (21), (23) and (24), I find

$$W\{r_2,r_1\}\frac{\partial^2}{\partial x^2}\left(E_e\frac{\partial X}{\partial t}+AX\right)=\frac{d^2r_1}{dx^2}W\left\{r_2,E_e\frac{\partial X}{\partial t}+AX\right\}-\frac{d^2r_2}{dx^2}W\left\{r_1,E_e\frac{\partial X}{\partial t}+AX\right\}-W^2\{r_2,r_1\}X \tag{26}$$

with the boundary conditions

$$W\left\{r_1,E_e\frac{\partial X}{\partial t}+AX\right\}\Big|_{x=0}=0 \tag{27}$$

and

$$W\left\{r_1,E_e\frac{\partial X}{\partial t}+AX\right\}\Big|_{x=f}=0 \tag{28}$$

Since $X=1$ and $\frac{\partial X}{\partial t}=0$ at equilibrium, A satisfies

$$W\{r_2,r_1\}\frac{d^2A}{dx^2}-\left(\frac{d}{dt}W\{r_2,r_1\}\right)\frac{dA}{dx}+W\left\{\frac{dr_2}{dx},\frac{dr_1}{dx}\right\}A=-W^2\{r_2,r_1\} \tag{29}$$

with the boundary conditions

$$W\{r_1,A\}\Big|_{x=0}=0 \tag{30}$$

and

$$W\{r_2,A\}\Big|_{x=f}=0 \tag{31}$$

Therefore, on evaluating the Wronskians in (26), (27) and (28), I obtain

$$\left(1-\frac{1}{W}\frac{dA}{dx}\right)E_e\frac{\partial X}{\partial t}-\frac{Z}{W}\left[\frac{\partial^2}{\partial x^2}\left(E_e\frac{\partial X}{\partial t}\right)-\frac{1}{W}\left(\frac{dW}{dx}\right)\frac{\partial}{\partial x}\left(E_e\frac{\partial X}{\partial t}\right)\right]=\frac{\partial}{\partial x}\left(\frac{A^2}{W}\frac{\partial X}{\partial x}\right) \tag{32}$$

with the boundary conditions

$$\left[W\left\{r_1,E_e\frac{\partial X}{\partial t}\right\}+r_1A\frac{\partial X}{\partial x}\right]\Big|_{x=0}=0 \tag{33}$$

and

$$\left[W\left\{r_2,E_e\frac{\partial X}{\partial t}\right\}+r_2A\frac{\partial X}{\partial x}\right]\Big|_{x=f}=0 \tag{34}$$

where, W is used to abbreviate $W\{r_2, r_1\}$. Equation (32) with its boundary conditions (33) and (34) is completely equivalent to the original integral master equation (7) in the case where the kernel is separable in the form of Eq. (20). However, in the often realistic case of small transitions between receptor states per interaction time, A is small compared to W and $E_e\frac{\partial X}{\partial t}$ is small compared to A, resulting in the approximation

$$E_e\frac{\partial X}{\partial t}=\frac{\partial}{\partial x}\left(\frac{A^2}{W}\frac{\partial X}{\partial x}\right) \tag{35}$$

with boundary conditions

$$\left.\frac{\partial X}{\partial x}\right|_{x=0}=0 \text{ and } \left.\frac{\partial X}{\partial x}\right|_{x=f}=0 \tag{36}$$

Therefore, I again determine that in the limit of small transmissions between antibody-pathogen complex states, the time-dependent aggregate size distribution can be well-described by an ordinary diffusion equation.

Probability distribution for change in number of antibodies: To illustrate the usefulness of the new methodologies, I solve the diffusion equation (using the first method). To solve the diffusion equation a form for $R(x, x')$ is required. Consider the quantum version of antibody-pathogen interactions. In a time characteristic of the interaction of an antibody with an antigen, of duration δ_t, a bound site may dissociate with probability q or remain bound with probability 1-q. Here, q is related to the antibody's dissociation constant, k_D. Also, an antibody may attach to an unbound site with probability p or an unbound site may remain unbound with probability 1-p. Here, p is related to the antigen-antibody association rate, k_A. Then, it can be shown that:

$$P(i,j)=\sum_{k=\max\{i-j,0\}}^{\min\{f-j,i\}}\binom{v(i)}{j-i+k}\binom{i}{k}q^k(1-q)^{i-k}p^{j-i+k}(1-p)^{v(i)-(j-i+k)} \tag{37}$$

where, P(i,j) denotes the probability that a pathogen bound at i sites becomes a pathogen bound at j sites in one interaction time and v(i) is the valence (the number of sites remaining available for binding if i are already bound). Ignoring any spatial interference

$$v(i) = f\text{-}i \tag{38}$$

Here,

$$\sum_{j=0}^{N}P(i,j)=1 \tag{39}$$

as required. Since $\Gamma(n+1) = n!$, the analogous probability distribution for the approximate continuous distribution is used, namely,

$$P(x,x')=\int_{\max\{x+x',0\}}^{\min\{f+x,x\}}C(x,x')q^{\zeta}(1-q)^{x-\zeta}p^{x'-x+\zeta}(1-p)^{f-x'-\zeta}d\zeta, \tag{40}$$

Where, $C(x, x')$ is the number of ways a pathogen bound at x sites can become a pathogen bound at x′ sites and can be expressed as:

$$C(x,x')=\frac{\Gamma(f-x+1)\,\Gamma(x+1)}{\Gamma(f-x'-\zeta+1)\Gamma(x'-x+\zeta+1)\Gamma(\zeta+1)\Gamma(x-\zeta+1)} \tag{41}$$

An example of the probability distribution is illustrated in Fig. 1.

Then, $k(x, x') = k_1P(x, x')$, where k_1 is a rate parameter that incorporates the interaction time δ_t. The equilibrium distribution, $E_e(x)$, can now be determined according to eq. (5), namely,

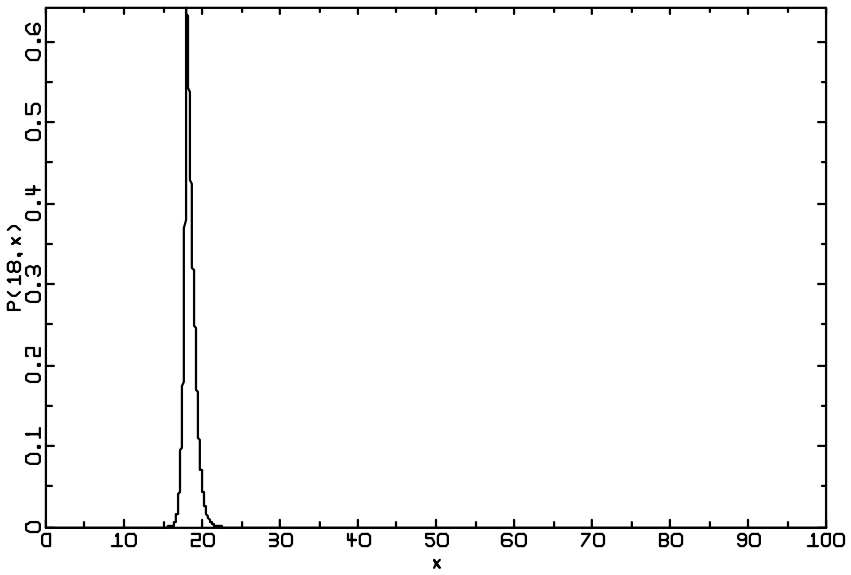

Fig. 1: A typical probability distribution for moving from one antibody level to another. Here, the probability of a pathogen bound with 18 antibodies becoming a pathogen bound by x antibodies in one interaction time is illustrates. Here, p = 0.005, q = 0.003 and f = 100

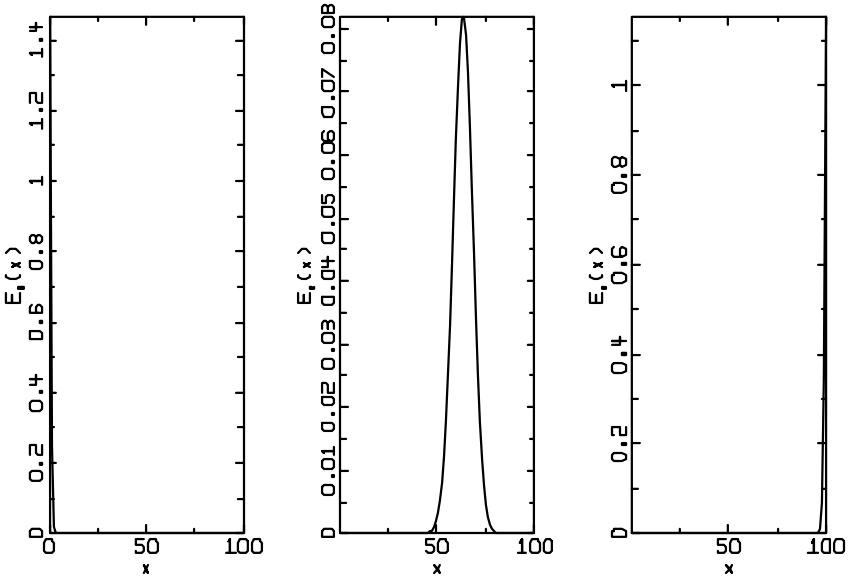

Fig. 2: Plots of the equilibrium distribution , $E_e(x)$. Here, $f_1 = f = 100$. (a) Binding probability low relative to dissociation probability (p = 0.00005, q = 0.03). (b) Binding probability comparable to dissociation probability (p = 0.005, q = 0.003). (c) Binding probability high relative to dissociation probability (p = 0.05, q = 0.0003)

$$E_e(x) = E_0\left[\int_0^f \frac{P(x,x')}{P(x',x)}dx'\right]^{-1} \tag{42}$$

which is illustrated in Fig. 2 for various probabilities, p and q.

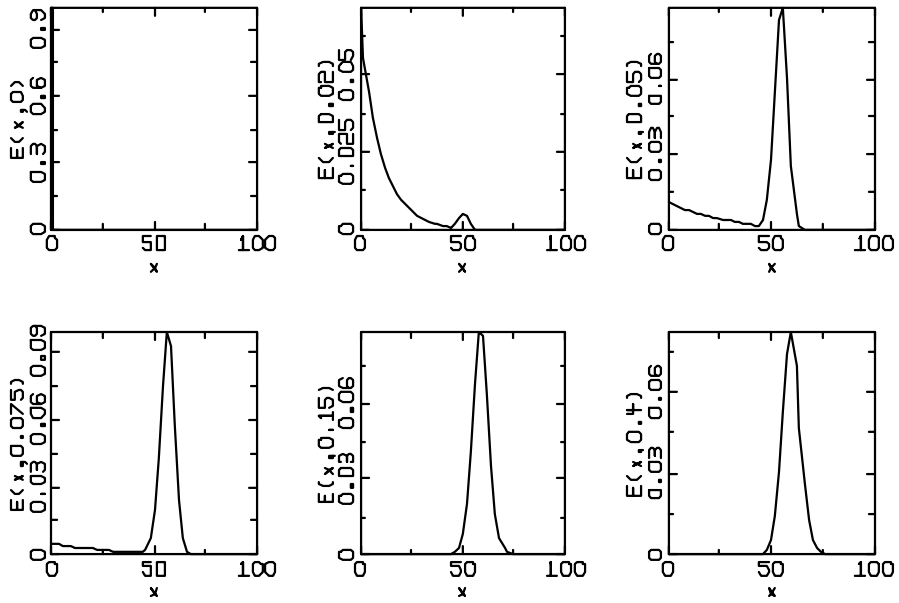

Fig. 3: Sequence of numerical solutions for E(x), the pathogen concentration of antibody distribution, for various times. Here, p = 0.005, q = 0.003

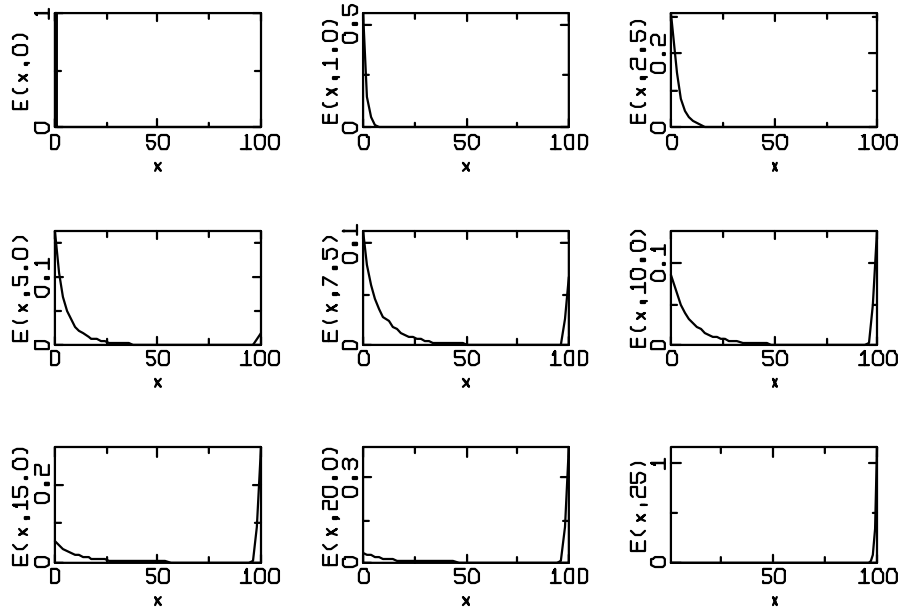

Fig. 4: Sequence of numerical solutions for E(x), the pathogen concentration of antibody distribution, for various times. Here, p = 0.05, q = 0.0003

In the limiting case as $p \to 0$ (that is, antibodies do not attach to unbound sites because the antibody and ligand site are not complimentary),

$$E_e(x) = E_0\delta(x) \tag{43}$$

Where, $\delta(x)$ is the dirac delta function. Although the reaction of ligand-receptor binding is reversible, in particular cases of specific binding the dissociation reaction can be neglected [7]. Then in the limiting case as $q \to 0$ (that is, irreversible binding),

$$E_e(x) = E_0\delta(x - f) \quad (44)$$

Numerical solution: Given an expression for R(x, x́), an expression for the kernel of our diffusion equation can be determined, $\mu_2(x)$. The magnitude of the kernel function varies considerably with the probabilities for binding and dissociation. This greatly influences the time for diffusion. A fully implicit vertex-centred finite volume method is employed [11] to obtain numerical solutions to the one-dimensional diffusion equation, equation (17) and then equation (6) is used to revert to the solution for E(x,t), the concentration of pathogens with x antibodies attached at time t. Fig. 3 and 4 illustrate the solutions for E at various times, for two different expressions of the kernel, $\mu_2(x)$, corresponding to relative medium and large probabilities of antibody attachment. The solution for E is not displayed when the probability of antibody attachment is small because there is little change from the initial distribution.

CONCLUSIONS

The immune system is crucial in neutralizing many infectious agents and the humoral arm of the immune system is an example of the very important process of receptor interactions. The master equation for infectious particle-antibody levels in discrete and classical forms has been presented and two methods for how the classical master equation can be transformed to an equivalent diffusion equation in a non-dimensional variable has been demonstrated. Thus, a system of N (N usually very large) coupled ordinary differential equations has been reduced to a single diffusion equation. The diffusion equation is much easier to work with, is computationally efficient and the theory of such an equation is well-known. The theory is also generally applicable to many infectious particles.

ACKNOWLEDGMENTS

I would like to thank the tremendous support by Marina and Sammy Wilson.

REFERENCES

1. Dembo, M. and B. Goldstein, 1978. Theory of equilibrium binding of symmetric bivalent haptens to cell surface antibody: Application to histamine release from basophils. J. Immunol., 121: 345-353.
2. Posner, R.G., C. Wofsy and B. Goldstein, 1995. The kinetics of bivalent ligand-bivalent receptor aggregation: Ring formation and the breakdown of the equivalent site approximation. Math. Biosci., 126: 171-190.
3. Schweitzer-Stenner, R., I. Licht, I. Luscher and I. Pecht, 1987. Dimerization kinetics of the IgE-class antibodies by divalent haptens. II. The interaction between intact IgE and haptens. Biophys. J., 63: 563-568.
4. Perelson, A.S. and C. DeLisi, 1980. Receptor clustering on a cell surface. I. Theory of receptor cross-linking by ligands bearing two chemically identical functional groups. Math. Biosci., 49: 87-110.
5. Perelson, A.S., 1985. A model for antibody mediated cell aggregation: rosette formation In: Mathematics and computers in biomedical applications, Eisenfeld, J. and C. DeLisi, (Eds.). New York: Elsevier, pp: 31-37.
6. Bentz, J., S. Nir and D.G. Covell, 1988. Mass action kinetics of virus-cell aggregation and fusion. Biophys. J., 54: 449-462.
7. Surovtsev, I.V., I.A. Razumov, V.M. Nekrasov, A.N. Shvalov, J.T. Soini, V.P. Maltsev, A.K. Petrov, V.B. Loktev and A.V. Chernyshev, 2000. Mathematical modeling the kinetics of cell distribution in the process of ligand-receptor binding. J. Theor. Biol., 206: 407-417.
8. Stewart, P.L., C.Y. Chiu, S. Huang, T. Muir, Y. Zhao, B. Chait, P. Mathias and G.R. Nemerow, 1997. Cryo-EM visualization of an exposed RGD epitope on advenovirus that escapes antibody neutralization. EMBO J., 16: 1189-1198.
9. Su, H., G.J. Spangrude and H.D. Caldwell, 1991. Expression of Fc-?RIII on HeLa 229 cells: Possible effect on *in vitro* neutralization of Chlamydia trachomatis. Infect. Immun., 59: 3811-3814.
10. McKee, C.S., 1997. Detailed Balancing. Applied Catalysis A: General, 154: N2-N3.
11. Ohlberger, M. and C. Rohde, 2002. Adaptive finite volume approximations for weakly coupled convection dominated parabolic systems. IMA Journal of Numerical Analysis, 22: 253-280.