Modelling the Impact of Multiple Pro-inflammatory Cytokines Using Molecular Communication

Shivam Thakker*, Dhaval K. Patel†, *Member, IEEE*, Kathan S. Joshi‡,
Miguel López-Benítez§ *Senior Member, IEEE*
*†‡School of Engineering and Applied Science, Ahmedabad University, India
§Department of Electrical Engineering and Electronics, University of Liverpool, United Kingdom
§ARIES Research Centre, Antonio de Nebrija University, Madrid, Spain
Email:*†‡{shivam.t1, dhaval.patel, kathan.j}@ahduni.edu.in,§M.Lopez-Benitez@liverpool.ac.uk

***Abstract*—Motivated by various health care applications and many other novel fields of Molecular Communication (MC), it has become an important field of research since the last decade. This paper proposes a molecular communication-based model for the spread of the SARS-CoV2 virus in the human body. The virus uses the ACE2 receptor as a gateway to enter the blood vessels, organs and then replicate itself. In response to the infection, the immune system synthesizes pro-inflammatory cytokines such as IL6, IL2, and $TNF\alpha$. This active bodily response may be further compromised by the generation of anti-inflammatory cytokines such as IL4 and IL10. We also propose a mathematical model using a Markov state transition for a flow-based molecular communication system which contributes to the detection of these pro-inflammatory cytokines level and gives a further inference about the infection in the body by taking multiple cytokines into account.**

***Index Terms*—Flow-Based Molecular Communication System, Multiple Cytokines, Markov State Transition Model, COVID-19, Disease Detection, Cytokine Storm**

I. Introduction

The global pandemic caused by the SARS-CoV2 virus has been a major cause of death in the past few years. The methods to counteract spread of the diseases and contain the inflammation is in spotlight of recent research activities. The virus is continuously evolving from its core consisting of zoonotic RNA by being encapsulated in a protein spike envelope. The virus infiltrates human body mainly through nasal cavity, but it could also enter through gastro-intestinal tract. Viruses further pass through respiratory tract, and ends up being binded by the host cells known as angiotensin-converting enzyme or ACE2 receptor [1]. The ACE2 receptor serves as an entry gateway for the internalization of SARS-COV-2 virus located on the epithelial alveolar lining, and in organs such as heart, liver, kidney, etc. which eventually leads to organ failure [2]. The viruses spike of glycoprotein (s) carries high attraction towards the ACE2 receptors. The spike has two fundamental functional units from which one leads to binding effect with ACE2 receptor and other contributes to the internalization through membranes fusion [3]. Membranes fusion triggers the release of SARS-COV-2's RNA, which stimulates viral replication [4].

After internalization of the virus, bodily immune system may react by synthesizing pro-inflammatory cytokines such as IL6, IL2, and $TNF\alpha$ [5] [6]. This scenario may be further compromised by generation of anti-inflammatory cytokines such as IL4 and IL10 [7] [8]. High spread of infection leads to the rapid generation of pro-inflammatory cytokine, which is clinically known as Cytokine Storm [9]. It leads to serious repercussions in diseases spread, and organ damage such as observed lung lesions in COVID-19 disease [2] [10].

The role of IL10 is quite arguable. It acts as both pro-inflammatory and anti-inflammatory depending upon the conditions. Here the IL6 molecule generally binds with IL-6R or s-IL6R, which is a soluble form of IL-6R expressed by specific cells in plasma. This complex forms bond with gp130 and further carries intracellular signalling [11] [12] [13]. The complex formed by IL6/IL-6R and gp130 activates multiple intracellular signaling pathways for IL6 to be transmitted, which triggers systemic hyper-inflammation (SI), and synthesis of pro-inflammatory cytokines IL2, IL4, IL10, $TNF\alpha$. The blood vessels also get damaged due to this cytokine storm and eventually lead to cardiac load and coagulation which finally leads to thrombosis on thin vessels.

Molecular Communication (MC) is a novel emerging field, which is still at the crux of its interdisciplinary engineering applications. It studies the communication among entities such as molecules, Bio-Nano Things (BNTs), etc [14]. The research aims to help doctors with the expertise of the computer science field by applying molecular communication. It has been inferred from the previous research that IL6 and IL10 or IL10 and $TNF\alpha$ together perform better in estimating the inflammation level in the body as compared to a single cytokine IL6 molecule [15].

A. Motivation

The main motivation behind this paper is that to date, there are very few papers discussing multiple cytokines for disease detection with molecular communication. Unlike [6] which only considers IL6 molecules for disease detection. Also, some of the papers have tried using multiple cytokines but through blood samples and not molecular communication [15] [16] . The main disadvantage of the blood test and the Reverse transcriptase-polymerase chain reaction (RT-PCR) is that these tests are carried out after symptoms such as fever, breathing difficulty, cough, weakness, etc. are noticed. Additionally, the results may also vary by test specimens [17]. The test results are

inconsistent for some specimens taken from the same patient [18] [19]. Hence, RT-PCR may not always detect infection with precision. This problem is further elevated in the case of cancer where symptoms are experienced after the 3^{rd} or 4^{th} stage of disease progression. Whereas the advantage of using molecular communication as compared to RT-PCR or blood tests is that using molecular communication we get an early prediction of disease by analyzing the change in levels of cytokines and classifying it according to the thresholds decided for any particular disease. Hence, we are trying to incorporate multiple cytokines for the COVID-19 disease detection by giving the levels or the concentration of these cytokines in the body using molecular communication. For this, we have proposed a flow-based molecular communication system emulating a real-life scenario of a blood vessel. In the model, we have considered co-related biological processes behind the attack of SARS-CoV2 to reduce the false-negative error prevailing in previous works and to detect the COVID-19 infection. This model could also be used for the detection of many major diseases like heart attack and cancer by just knowing the concentration of cytokines related to these diseases.

By incorporating this model we can get an accurate result and can also save the lives of people by early predicting the deadly disease like cancer, COVID-19, or heart attack and providing timely treatments. We can also estimate the concentration of these cytokines and predict whether the disease is benign or malignant depending upon the thresholds of the cytokines used. It can also be used to monitor the sugar level for diabetic patients, heartbeats, cholesterol level, and many more. Therefore the methods using molecular communication are far better as they give a continuous level of these cytokines and help in disease detection at a very early stage. Hence this could be a huge field to work on and has a great potential in the future.

B. Contribution

In particular, the main contribution of this paper is as follow:

Firstly we propose a Markov state transition model considering multiple cytokines as a ligand forming bonds with the receptors. In the proposed model we mention the current state of the Markov model based on the multiple cytokines and antibodies bond formation with the receptor. We estimate the absorption probability of any particular molecule to form a bond with the receptor, as only a single molecule can bind to a receptor at a time.

Secondly we study the detection of excessive levels of inflammatory cytokines considering multiple transmitted cytokines. We try to show the effect on the average bond formed by antibodies concerning their arrival rate and concentration. We also evaluate the number of cytokine bonds to estimate the inflammation level accordingly.

The main aim of this paper is to provide a Molecular Communication system for the detection of COVID-19 disease by contemplating the existence of multiple cytokines. We propose a mathematical model to estimate the level of inflammation for COVID-19 disease prediction by considering the cytokines responsible for COVID-19. The paper is organized as follows: Section II includes the Biological background which co-relates multiple cytokines with COVID-19. Section III includes the System Model which describes the absorption process of the cytokines by the receptor and the Markov model for multiple cytokines. Section IV includes numerical results for the analytical model generated in Matlab. Section V includes the Conclusion and the future work.

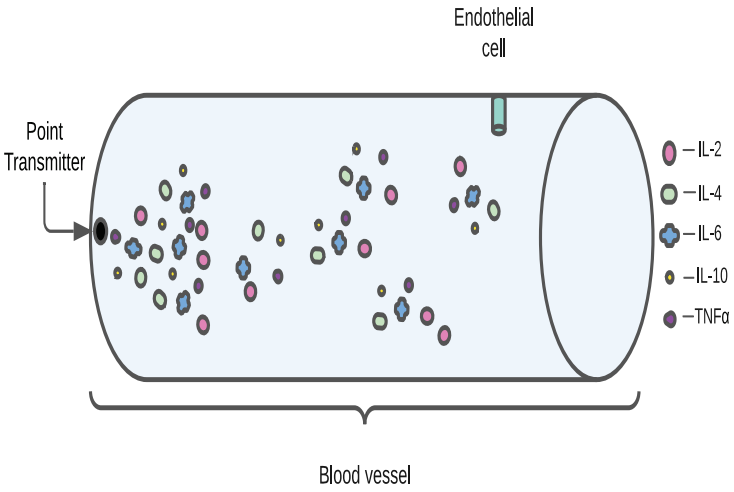

Fig. 1: The Network Model

II. System model

In this section we centralize the concept of absorption process of multiple cytokines with the gp130 receptor and describe the Markov state transition model behind it. We propose a flow based molecular communication system emulating the scenario of a blood vessel.

The considered network model contemplates the presence of single multi-ligand based receptor compliant with all the considered cytokines. Fig. 1 describes the network model, which emulates real scenario of a small portion of blood vessel with Red Blood Cells (RBCs) and considers multiple cytokines.

In particular, our model considers the following assumptions:

- A1: The network model assumes a cylindrical structure as blood vessel.
- A2: The model assumes laminar flow in the blood vessels.
- A3: A single point transmitter is assumed to be able to transmit all the considered cytokines.
- A4: The molecules transmitted by the transmitter diffuses freely in Brownian motion.
- A5: We assume that a single molecule can only bind to a single receptor at a time.
- A6: Each collision of molecules carries sufficient energy to form a bond with the receptor.

For simplicity, we have assumed the cytokines to be transmitted by a single point transmitter instead of being transmitted by T-cells as a part of the immune system. The cytokines diffuse under the effect of laminar flow [20] and bind with the surface receptors present on the endothelial lining of the emulated blood vessel. We have considered co-related biological processes behind the attack of SARS-CoV2 to reduce

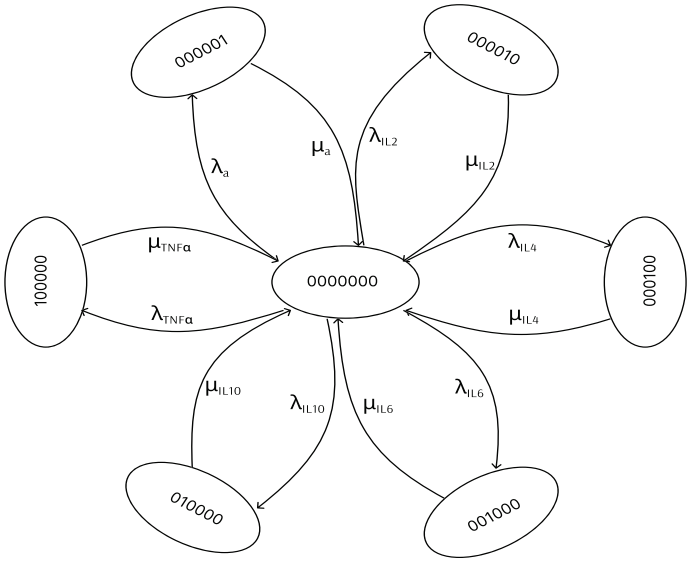

Fig. 2: Markov State Transition model

the false-negative error and to detect the COVID-19 infection. We consider that multiple cytokines such as IL6, IL2, IL4, IL10, and $TNF\alpha$ are transmitted from a point transmitter and absorbed by a multi-ligand receptor present in the considered section. We can also evaluate the concentration of antibodies required to counteract the inflammation by making a bond with IL-6R receptors exposed by the endothelium and inhibiting the bond formation with inflammatory cytokines.

The main aim of this monitoring system is to constantly check the levels of inflammatory cytokines to provide timely detection of the disease by perceiving the concentration of cytokines absorbed by the receiver. Following reactions undergo at the reception site:

$$[\mathrm{x}] + [\mathrm{gp}_{130}] \underset{\mathrm{k_{off,x}}}{\overset{\mathrm{k_{on,x}}}{\rightleftharpoons}} [\mathrm{y}] \tag{1}$$

$$[\mathrm{a}] + [\mathrm{gp}_{130}] \underset{\mathrm{k_{off,a}}}{\overset{\mathrm{k_{on,a}}}{\rightleftharpoons}} [\mathrm{z}] \tag{2}$$

x = IL2 , IL4, IL6, IL10, $TNF\alpha$

Here $k_{\mathrm{on,x}}$ and $k_{\mathrm{on,a}}$ are the on-rates of the cytokines and antibodies respectively and $k_{\mathrm{off,x}}$ and $k_{\mathrm{off,a}}$ are their corresponding off-rates. On-rates are the rates at which a ligand makes a bond with the receptor and off rates are reversible rates for the reactions. The complex y is formed by the reaction of all the cytokines x and gp130 and z is a complex formed by the reaction between an antibody molecule and the receptor. The receptor gp130 is compliant to make bonds with both the cytokines and the antibodies respectively. The reversibility of the formed bond is limited to a certain extent depending on the off-rates. Hence, new molecules may bind to the receptor once the preformed bond breaks.

The on-rates $k_{\mathrm{on,x}}$, $k_{\mathrm{on,a}}$ depend on the frequency of collision of these molecules with the receptors. Higher the frequency of collision, higher the on-rate. The off-rates of any complex are inversely proportional to their average lifetime τ [21]. The off rate of any molecule is as follows:

$$k_{\mathrm{off,i}} = \frac{1}{\tau}, i = x, a \tag{3}$$

TABLE I: On and off rates of the cytokines

Cytokines	$\mathrm{k_{on}}(M^{-1}s^{-1})$	$\mathrm{k_{off}}(s^{-1})$	Reference
IL6	$2.1{\cdot}10^{5}$	$2{\cdot}10^{-3}$	[22]
IL2	10^{7}	10^{-4}	[23]
IL4	$1.6{\cdot}10^{6}$	$2.1{\cdot}10^{-3}$	[24]
IL10	$1.8{\cdot}10^{6}$	$4.4{\cdot}10^{-4}$	[25]
TNFα	10^{6}	$5.76{\cdot}10^{-5}$	[26]

TABLE II: State Transition for the Markov Model

State	Molecules
000000	Free
000001	Antibody
000010	IL2
000100	IL4
001000	IL6
010000	IL10
100000	$TNF\alpha$

III. Proposed Markov model for multiple cytokines

We have considered that each receptor can make only a single bond at a time and can bind with either the antibody molecule or the cytokines. Hence we can model our receptor as a random process $\{n(t) = [n_{\mathrm{mol}}(t), n_a(t)], t \geq 0\}$ which is a continuous-time Markov process with $n_i(t) \in \{0, 1\}$, [6] for i = mol,a and mol = IL2, IL4, IL6, IL10, $TNF\alpha$.

We can say that $n_{\mathrm{mol1}}(t) + n_{\mathrm{mol2}}(t) + n_{\mathrm{mol3}}(t) + n_{\mathrm{mol4}}(t) + n_{\mathrm{mol5}}(t) + n_a(t) \leq 1$. Here mol represents all the cytokines like IL2, IL4, IL6, IL10 and $TNF\alpha$. Fig. 2. depicts all the possible state transitions for the cytokines IL2, IL4, IL6, IL10, $TNF\alpha$, and the antibodies bonds respectively. The markov model probabilistically emulates the reception process of the multiple cytokines at the receptor as per the arrival rate (λ) and the off rate (μ). Hence the states that are possible in this condition are shown in Table II.

The probability of binding with any cytokines molecule (mol) [6] would be as below where λ_{mol} indicates the bond formation rate or the arrival rate of each ligand and μ_{mol} indicates their off rate or the release rate of the ligand:

$$P_{\mathrm{mol}} = \frac{\lambda_{\mathrm{mol}}/\mu_{\mathrm{mol}}}{1 + \lambda_{\mathrm{mol}}/\mu_{\mathrm{mol}} + \lambda_{\mathrm{mol}}/\mu_{\mathrm{mol}}} \tag{4}$$

Here mol could be IL2, IL4, IL6, IL10, $TNF\alpha$, and antibody a.

Considering the concentration of multiple cytokines at the receiver end, the probability of forming bond at each receptor with any two cytokines mol_1 or mol_2 would be:

$$\begin{aligned} P(mol_1 \cup mol_2) = P(mol_1) + P(mol_2) \\ - P(mol_1 \cap mol_2) \end{aligned} \tag{5}$$

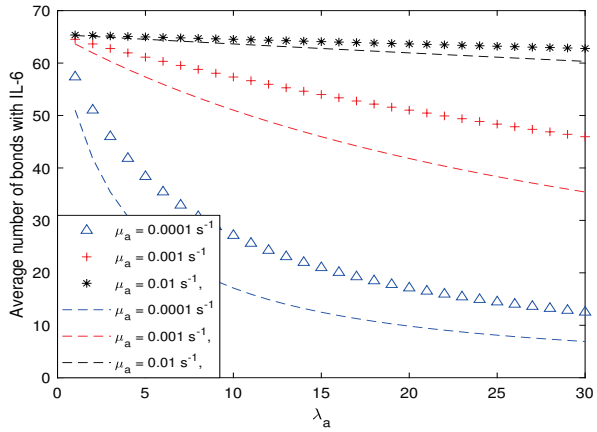

Fig. 3. Average number of IL6 bonds

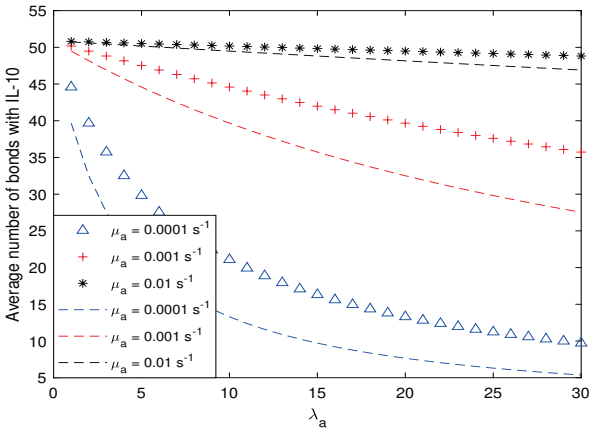

Fig. 4.Average number of IL10 bonds

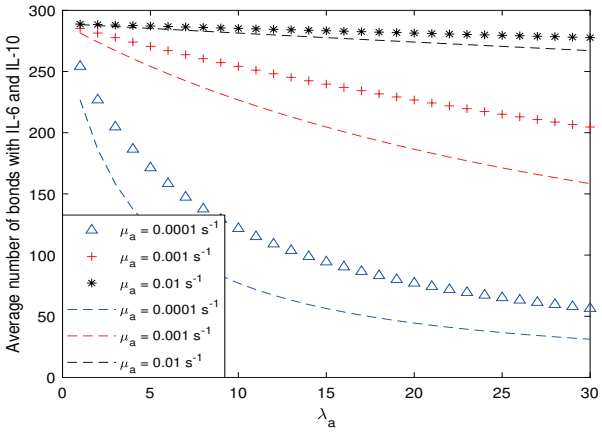

Fig. 5. Average number of bonds with IL6 and IL10

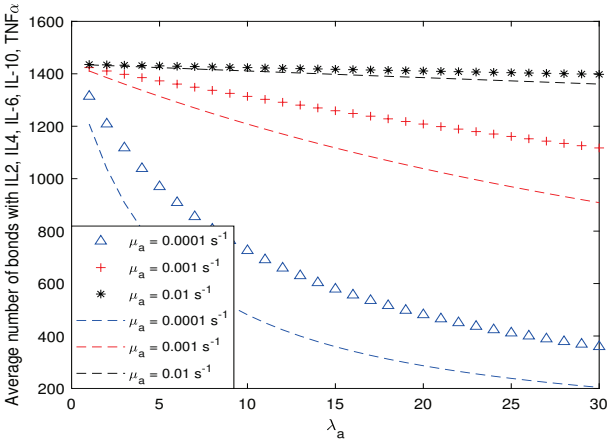

Fig. 6. Average number of bonds with all cytokines

Here as the probability of bond formation by one molecule is independent to other, we can write it as:

$$P_{(mol_1 \cup mol_2)} = P_{mol_1} + P_{mol_2} - (P_{mol_1} * P_{mol_2})$$

Hence in general if we want to find the probability for n cytokines we can calculate it by,

$$P(\bigcup_{i=1}^{n} mol_i) = P((\bigcup_{i=1}^{n-1} mol_i) \cup mol_n)$$

$$= \mathrm{P}(\bigcup_{i=1}^{n-1} mol_i) + P(mol_n) - P((\bigcup_{i=1}^{n-1}(mol_i \cap mol_n))$$

$$= \sum_{k=1}^{n} (-1)^{k+1} \sum_{1 \le i_1 < \ldots < i_k \le n} P(\bigcap_{j=1}^{k} mol_{i_j}) + P(mol_n)$$

$$- \sum_{k=1}^{n} (-1)^{k+1} \sum_{1 \le i_1 < \ldots < i_k \le n-1} P(\bigcap_{j=1}^{k} mol_{i_j} \cap mol_n)$$

$$= \sum_{k=1}^{n} (-1)^{k+1} \sum_{1 \le i_1 < \ldots < i_k \le n} P(\bigcap_{j=1}^{k} mol_{i_j}) \quad (6)$$

From (6), we can calculate the probability of n cytokines to make a bond. The probability(P_x) of bond formation with any cytokine or antibody is mentioned in (4) and the arrival rate can be calculated by the multiplication of $k_{\mathrm{on,i}}$ i.e the on rate of any ligand i and the concentration c_i of ligand i close to the considered receptor [27]. We here assume that the concentration of these ligands is uniform near the vessel wall. So the arrival rate λ can be given as :

$$\lambda_i = k_{on,i} * c_i(t) \quad (7)$$

The number of receptors that bind to the cytokines can be modelled through a Binomial distribution. Each cell has N_r receptors and they are occupied by the cytokines with probability P_x. Hence the average number of bonds or the average number of receptors busy with these cytokines can be given as [6]:

$$R_c = N_r * P_{mol} \quad (8)$$

Here the number of receptors that we are considering is 2000 [6]. Using (8) we can calculate the number of bonds formed by the inflammatory cytokines as the product of the number of receptors and their absorption probability. By calculating the number of bonds formed by the inflammatory cytokines, we can estimate the inflammation level in a human body. The higher number of bonds formed with the cytokines, indicates higher inflammation level in the human body.

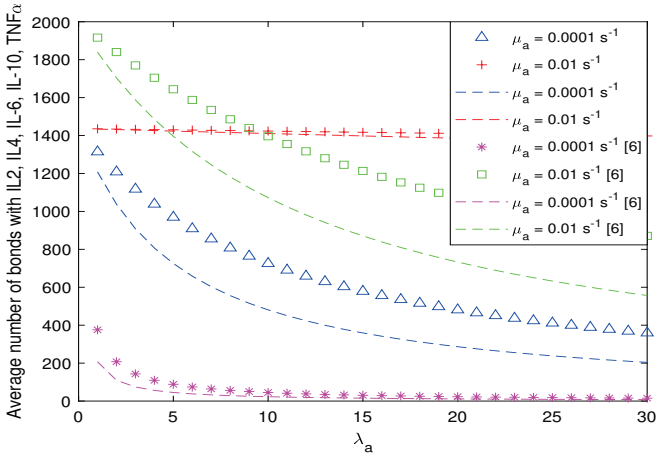

Fig. 7. Backward Compatibility for average number of bonds

IV. Numerical Results

We have shown the effect of using multiple cytokines for more accurate detection of inflammation levels in the body. We have used (8) in order to get the average number of bonds formed by the cytokines. Depending upon the arrival rate of the antibody molecule, we have tried to plot the average number of bonds formed by a particular cytokine on the Y-axis and the arrival rate of antibody on the X-axis. We have generated different graphs by taking different values of off-rates of antibody to derive mentioned contributions.

From Figs. 3 and 4 we can observe that the maximum number of bonds as a function of arrival rate of antibody molecules formed by the IL6 and IL10 is around 65 and 50 and the minimum bonds formed are 6.90 and 5.36 respectively which is much lower. So using only single molecule would not give us better accuracy. Also from the figures we can see that as the arrival rate of the antibody increases, the average number of bond decreases. The off rate of antibody is lower as compared to the cytokines and so less bonds are formed.

The different values of arrival rate for all the cytokines that are used in Figs. 3, 4, 5, 6, and 7 are shown in Table III. From the Fig. 5 we can observe that using both IL6 and IL10 as the transmitted molecules, the average number of bonds with cytokines as a function of antibodies arrival rate increases rapidly up to 288 and the minimum number of bonds formed is around 31.2.

From Fig. 6 we can observe that on using 5 cytokines together, the number of absorbed molecules jumped to 1434 which is a very huge number and its minimum bonds formed were 204. It is advantageous to use multiple cytokines since it results in a higher number of bonds formed compared to a single cytokine and therefore it gives us a better accuracy. As we know that all the types of cytokines can form bonds with the receptor, if we consider only a single cytokine it would generate a large number of false negative errors as it will show very less bonds which is observed in Figs. 3 and 4.

Whereas in real life scenario, there would be much more bonds formed by the receptor and the inflammation would have grown significantly.

TABLE III: Arrival rates and off rates of the cytokines

Cytokines	Arrival rate $(\lambda)(s^{-1})$	Off rate $(\mu)(s^{-1})$
IL6	4.63, 2.315	$2{\cdot}10^{-3}$
IL2	2.4, 1.2	10^{-4}
IL4	3.2, 1.6	$2.1{\cdot}10^{-3}$
IL10	3.6, 1.8	$4.4{\cdot}10^{-4}$
TNFα	2, 1	$5.76{\cdot}10^{-5}$

So using multiple cytokines, we can accurately infer about the inflammation of COVID-19 at a very early stage. This model could be applied for several other types of disease like diabetes to know the sugar level, cancer, heart attack by just knowing the concentration of cytokines related to that disease.

From Fig. 7 we can deduce that unlike [6] which only considered IL6 molecule, the average number of cytokine bonds gives false positive error as only IL6 cannot predict the disease severity for COVID-19 disease. While in real life scenario, the severity of any disease is not dependent on only one cytokine, it is a collective dependency between many other cytokines for any particular disease [15]. Hence, our proposed model by considering multiple cytokines related to COVID19 has the potential to overcome the drawbacks of [6].

Finally, we deduce that by keeping the off-rate of antibody constant and reducing the arrival rates of cytokines by half, the average number of bonds formed is decreased significantly. So from this we can infer that almost half dose of antibodies could counteract the spread. The large dose may also affect human health adversely. Thus, the dose of antibodies must be just sufficient to contain the spread of inflammation, which is decreased by considering our proposed model unlike previous attempts with single cytokine.

V. Conclusion and Future Work

The proposed molecular communication system, provides a new direction for the detection of inflammatory levels by contemplating multiple cytokines. The proposed method provides more accurate results as compared to the previous research which considers single cytokine. This method is applicable to many diseases to detect their severity by considering the level of

cytokines in the body. In this paper we have showed that using multiple cytokines can reduce the false negative rate that was occurring earlier considering only a single cytokine. Also only the levels of IL6 cannot be considered to predict the disease severity for COVID19 as the concentration of IL6 varies with all the diseases that cause inflammation. Hence we should focus on using multiple cytokines for all the diseases to get better and more accurate results.

We have proposed a general system which is applicable for an arbitrary number of cytokines. As the proposed Markov model can be generalized for n different cytokines, the future research could be the application of our proposed model for multiple diseases by determining the co-related cytokines for that particular disease.

REFERENCES

[1] C. Koca, M. Civas, S. M. Sahin, O. Ergonul, and O. B. Akan, "Molecular communication theoretical modeling and analysis of SARS-CoV2 transmission in human respiratory system," *IEEE Transactions on Molecular, Biological and Multi-Scale Communications*, vol. 7, no. 3, pp. 153–164, 2021.

[2] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong *et al.*, "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China," *Jama*, vol. 323, no. 11, pp. 1061–1069, 2020.

[3] S. K. Saxena, S. Kumar, P. Baxi, N. Srivastava, B. Puri, and R. Ratho, "Chasing COVID-19 through SARS-CoV-2 spike glycoprotein," pp. 399–407, 2020.

[4] S. Kumar, R. Nyodu, V. K. Maurya, and S. K. Saxena, "Morphology, genome organization, replication, and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)," in *Coronavirus Disease 2019 (COVID-19)*. Springer, 2020, pp. 23–31.

[5] K. Ashalatha, Y. Venkateswarlu, A. M. Priya, P. Lalitha, M. Krishnaveni, and S. Jayachandran, "Anti inflammatory potential of decalepis hamiltonii (wight and Arn) as evidenced by down regulation of pro inflammatory cytokines—TNF-α and IL-2," *Journal of ethnopharmacology*, vol. 130, no. 1, pp. 167–170, 2010.

[6] L. Felicetti, M. Femminella, and G. Reali, "A molecular communications system for the detection of inflammatory levels related to COVID-19 disease," *IEEE Transactions on Molecular, Biological and Multi-Scale Communications*, vol. 7, no. 3, pp. 165–174, 2021.

[7] J. Z. Kawalkowska, T. Hemmerle, F. Pretto, M. Matasci, D. Neri, and R. O. Williams, "Targeted IL-4 therapy synergizes with dexamethasone to induce a state of tolerance by promoting treg cells and macrophages in mice with arthritis," *European journal of immunology*, vol. 46, no. 5, pp. 1246–1257, 2016.

[8] H. Islam, T. C. Chamberlain, A. L. Mui, and J. P. Little, "Elevated interleukin-10 levels in COVID-19: potentiation of pro-inflammatory responses or impaired anti-inflammatory action?" *Frontiers in Immunology*, p. 2485, 2021.

[9] E. A. Coomes and H. Haghbayan, "Interleukin-6 in covid-19: a systematic review and meta-analysis," *Reviews in medical virology*, vol. 30, no. 6, pp. 1–9, 2020.

[10] L. Tang, Z. Yin, Y. Hu, and H. Mei, "Controlling cytokine storm is vital in COVID-19," *Frontiers in Immunology*, p. 3158, 2020.

[11] M. Iwasaki, J. Saito, H. Zhao, A. Sakamoto, K. Hirota, and D. Ma, "Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: molecular mechanisms and implications," *Inflammation*, vol. 44, no. 1, pp. 13–34, 2021.

[12] S. Kang, T. Tanaka, H. Inoue, C. Ono, S. Hashimoto, Y. Kioi, H. Matsumoto, H. Matsuura, T. Matsubara, K. Shimizu *et al.*, "IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome," *Proceedings of the National Academy of Sciences*, vol. 117, no. 36, pp. 22 351–22 356, 2020.

[13] T. Tanaka, M. Narazaki, and T. Kishimoto, "Il-6 in inflammation, immunity, and disease," *Cold Spring Harbor perspectives in biology*, vol. 6, no. 10, p. a016295, 2014.

[14] S. Pal, N. Islam, and S. Misra, "Vivid: In vivo end-to-end molecular communication model for COVID-19," *IEEE Transactions on Molecular, Biological and Multi-Scale Communications*, vol. 7, no. 3, pp. 142–152, 2021.

[15] L. Dizdarević-Hudić, Z. Kušljugić, F. Baraković, S. Brkić, D. Sabitović, E. Jahić, M. Isabegović, E. Smajić, I. Hudić, and K. Divković, "Correlation between interleukin 6 and interleukin 10 in acute myocardial infarction," *Bosnian journal of basic medical sciences*, vol. 9, no. 4, p. 301, 2009.

[16] S. K. Dhar, K. Vishnupriyan, S. Damodar, S. Gujar, and M. Das, "IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression," *Heliyon*, vol. 7, no. 2, p. e06155, 2021.

[17] W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, and W. Tan, "Detection of SARS-CoV-2 in different types of clinical specimens," *Jama*, vol. 323, no. 18, pp. 1843–1844, 2020.

[18] S. A. Kujawski, K. K. Wong, J. P. Collins, L. Epstein, M. E. Killerby, C. M. Midgley, and G. R. Abedi, "Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the united states," *Nature medicine*, vol. 26, no. 6, pp. 861–869, 2020.

[19] R. Wölfel, V. M. Corman, W. Guggemos, M. Seilmaier, S. Zange, M. A. Müller, D. Niemeyer, T. C. Jones, P. Vollmar, C. Rothe *et al.*, "Virological assessment of hospitalized patients with COVID-2019," *Nature*, vol. 581, no. 7809, pp. 465–469, 2020.

[20] L. Felicetti, M. Femminella, and G. Reali, "Simulation of molecular signaling in blood vessels: Software design and application to atherogenesis," *Nano Communication Networks*, vol. 4, no. 3, pp. 98–119, 2013. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1878778913000306

[21] J. Corzo, "Time, the forgotten dimension of ligand binding teaching," *Biochemistry and Molecular Biology Education*, vol. 34, no. 6, pp. 413–416, 2006.

[22] A. Hammacher, R. J. Simpson, and E. C. Nice, "The interleukin-6 (IL-6) partial antagonist (q159e, t162p) IL-6 interacts with the IL-6 receptor and gp130 but fails to induce a stable hexameric receptor complex," *Journal of Biological Chemistry*, vol. 271, no. 10, pp. 5464–5473, 1996.

[23] D. J. Stauber, E. W. Debler, P. A. Horton, K. A. Smith, and I. A. Wilson, "Crystal structure of the IL-2 signaling complex: paradigm for a heterotrimeric cytokine receptor," *Proceedings of the National Academy of Sciences*, vol. 103, no. 8, pp. 2788–2793, 2006.

[24] X. Wang, P. Lupardus, S. L. LaPorte, and K. C. Garcia, "Structural biology of shared cytokine receptors," *Annual review of immunology*, vol. 27, pp. 29–60, 2009.

[25] S. I. Yoon, B. C. Jones, N. J. Logsdon, B. D. Harris, S. Kuruganti, and M. R. Walter, "Epstein-barr virus IL-10 engages IL-10R1 by a two-step mechanism leading to altered signaling properties," *Journal of Biological Chemistry*, vol. 287, no. 32, pp. 26 586–26 595, 2012.

[26] J. O'Connell, J. Porter, B. Kroeplien, T. Norman, S. Rapecki, R. Davis, D. McMillan, T. Arakaki, A. Burgin, D. Fox III *et al.*, "Small molecules that inhibit tnf signalling by stabilising an asymmetric form of the trimer," *Nature communications*, vol. 10, no. 1, pp. 1–12, 2019.

[27] M. Pierobon and I. F. Akyildiz, "Noise analysis in ligand-binding reception for molecular communication in nanonetworks," *IEEE Transactions on Signal Processing*, vol. 59, no. 9, pp. 4168–4182, 2011.