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Article - Human and Animal Health

A Theoretical Essay on Interactions of SARS-CoV-2 Infection with Chronic Obesity Inflammation: an Application of Theoretical Knockouts

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HIGHLIGHTS

- Obesity inflammation and covid-19.
- Double inflammation crosstalk interactions.
- Inflammation network in covid-19.

Abstract: Pathophysiological characteristics of obesity includes chronic inflammation. Complications in the respiratory tract are related to bodily problems, which lead to a restriction of lung function due to reduced volume, inducing an increase in respiratory work. SARS-CoV-2 has a high potential for contamination by respiratory secretions and, therefore, obesity is one of the main risk factors for complications. The relations between obesity and SARS-CoV-2 are complex, since the immunological agents that are activated by these processes are ubiquitous. It is well-known that network analysis can generate results about the dynamics of complex biological phenomena, such as signalling networks, neural networks, immunological networks, and so on. Here we propose and analysis and interpretation of the complex relationships between obesity and COVID-19 in a meta-analysis study using complex network modelling and the theoretical knockouts technique. In a complex network of this kind, vertices are considered as immunological agents and their relation as directed edges. We built two networks: one related to COVID-19 and obesity (synergy) and another only with COVID-19. In both networks, we have performed the knockout of all 52 vertices. These knockouts indicated that, besides the Infected Host Cell and COVID viral particle, IL-17; CD40, AR and AL

channels; and Th17, were the most relevant agents in this complex network. Overall, our study indicated the superior role and importance of IL-17 in this context. Such result corroborates with the role of IL-17 in identification and prognosis of Acute Respiratory Discomfort Syndrome (ARDS).

Keywords: cytokines; inflammation; Obesity; respiratory system; SARS-CoV-2.

INTRODUCTION

Obesity is one of the biggest public health problems in the our contemporary time. The World Health Organization (WHO) projected for 2025 about 2.3 billion overweight adults and more than 700 million obese with significant growth in Western Countries. In the United States of America (USA), the prevalence of obesity has risen from 23% to almost 40% in recent years whereas in the United Kingdom, it has increased by approximately 10% in 25 years [1,2].

Pathophysiological aspects of the obese include chronic inflammation hallmarked by increased levels of circulating acute inflammatory cytokines, IL-6, TNF-α, CRP (C-reactive protein), haptoglobin, IL-1b, IL-8 and IL-10. This chronic inflammatory state aggravates the symptoms favoring the development of associated diseases, such as dyslipidemia, metabolic syndrome, diabetes, hypertension, asthma and bronchitis [3].

Complications in the respiratory tract are related to body issues, which lead to a restriction of lung function due to reduced volume, unrelated effects of lung and bronchi, inducing an increase in respiratory work, expansion of thorax, obstruction to airflow and decreased peripheral oxygen saturation. In addition, we have an inflammatory response that works synergistically aggravating the asthma, bronchitis and pneumonia [4-7].

In late 2019, it was described in Wuhan, China, that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes pandemic Coronavirus Disease (COVID-19), with high potential for contamination through respiratory secretions [8]. SARS-CoV-2 identified by a new RNA involved in the β-coronavirus, similar to SARS-CoV [9-10] has caused thousands of deaths worldwide [11]. Initially, the majority of those affected by the complications shown in relation to age, being mainly elderly due to the presence of comorbidities, which is associated with infections caused by the virus, increases the lethality, in the same way observed if the obese manifest the same or greater risk [12,13].

During the H1N1 epidemic, diabetic and obese people were considered more susceptible to the risk of contamination and individuals with a BMI ≥ 40 kg/m had a higher degree of complications [14]. Thus, this situation is repeated again, where obese individuals were directly correlated with complications of COVID-19, such as necessity of hospitalization and intensive care, sometimes, probably due to the increased risk associated with the chronic diseases resulted of obesity [15].

Thereby, the ratio of the hospitalization rate among the patients identified with COVID-19 was 4.6 per 100,000 inhabitants in the USA, in which the rates were higher (13.8) among adults aged ≥ 65 years, of whom 89.3% had one or more underlying conditions, with 48.3% being obese, in addition to conditions such as hypertension, chronic lung disease, diabetes mellitus and cardiovascular disease, which raise the levels of intensive care [16].

Indeed, obesity is considered a significant risk factor for COVID-19 complications [17], due to a severe crosslink between obesity, chronic inflammation, and respiratory infection. Considering the current health problem scenario and this strong tool to analyze complex networks, the major aim was to analyze the complex relations of obesity and COVID-19 in a meta-analysis study using complex network modeling and the theoretical knockouts technique [18]. Specifically we shall cover the following purposes: a) To build a network of interactions between the most immediate and relevant immunological agents that participates in the COVID-19 respiratory infection; b) To made a similar network with COVID-19 respiratory infection and the immunological factors considering the chronic inflammation state observed in obese patients; c) To calculate, using the Theoretical Knockouts Method (TKM), the relative importance of such immunological agents in such phenomena in both networks and compare the results of this method in order to quantify how obesity interferes in the COVID-19 infection in a metabolic level.

MATERIAL AND METHODS

The immunological agents are considered as vertices and their relations as directed edges in the network (*i.e.,* graph). In immunological networks there is two ways for those agents to interact: increasing or decreasing, so when the A increases the activation of agent B, then an arrow will originate from A and terminate in B. On the other hand, if A decreases the activation of B, then an arrow will originate from B and terminate in A [18].

Additionally, since matter and energy must be conserved in the resulting networks, we cannot allow any vertex to be a dead-end, that is, there is no biological agent without an exit in the system (*i.e.,* network). To deal with this situation, we insert in the network an origin and a terminus. All vertices that have no arrow (edge) entering it, will be connected to the origin – from the origin to these vertices. On the other hand, all vertices that have no arrow leaving it will be connected to the terminus – from these vertices to terminus. The origin and the terminus function as a section of a metabolic or an immunological phenomenon – that is, the zone of interest for analysis and knockouts. We cannot work with all possible interactions of the human body that COVID-19 and obesity influence. This is very reasonable, since only the local and most immediate have relevant and measurable impact in the phenomenon. Then, in a practical sense, both origin and terminus are considered as an environment for the purpose of our study. The environment consists in the set of less relevant interactions that we did not include in the network.

The production of IFN-α, IFNAβ and IFN-γ are one of the first innate responses to any viral infection. In this case, they are secreted by cells of the nasopharynx and bronchiolar mucosa. IFN-α and IFN-β are secreted primarily by the host cell infected, whereas IFNγ is initially produced by macrophages and NK cells [19,20]. NK cells are the main mediators of innate immunity and, in general, expand sufficiently to eliminate viruses in 4 to 6 days. These cells are stimulated by the three Interferons. The interaction between NK cells and infected host cell promotes increased secretion of IL-1, IL-2 and IFNγ by the host cell [21].

The viral RNA itself functions as a Pathogen-associated molecular patterns (PAMPS), stimulating, among other cells, macrophages that, in addition to phagocytic activities, will secrete a vast number of substances, among them: IL-1, IL-18 (which will increase secretion of IFNγ), IL-6, IL-12, TNF, NO, IL-10, IL-8. The association of IL-18 with IL-12 will promote a decrease in IL-4, which will lead to less IgE and IgG1. IL-8 will stimulate the phagocytic activity of Neutrophils associated with the complement C3b, which will cause the secretion of Myeloperoxidases, Defensin, Neutrophil elastase, Bacterial permeability-increasing protein (BPI), Cathepsin, Lactoferrin and Gelatinases [22,23].

Dendritic cells (DC) stimulated by the viral particle and interferons will activate CD4 + T cells. The interaction between DC and CD4 + T (CD40 - CD40L) will activate Tc (increased secretion of IFNγ, IL-10), B cells (secretion of TGF-β, Th17, IL-17 and IL-10) and DC licensing. Being an important step in the progression of the response to the viral agent [24,25]. Furthermore, chronic inflammation in obese patients is characterized by constitutive circulation of TNFα, IL-1b, IL-6, IL-8, TGF-β (leptin), IL-17 and IL-18, secreted by adipose tissue [26]. All the above stated interactions can be observed in the form of a complex network in Figure 1.

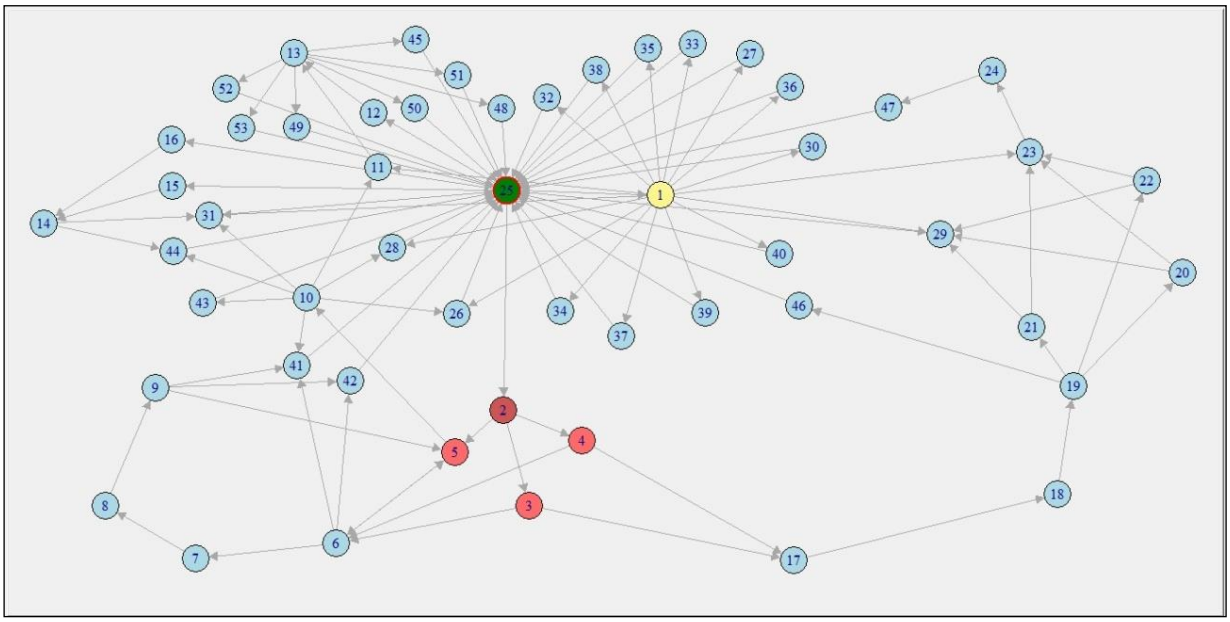

Figure 1. The network of immunological interactions for COVID-19 respiratory infection and chronic inflammatory state induced by obesity. Vertices labels: 1 – Adipose Tissue; 2 – COVID-19; 3 –IFNα; 4 – IFNβ; 5 – IFNγ; 6 – NK Cell; 7 – AR; 8 – AL; 9 – Infected Host Cell; 10 – Macrophage; 11 – IL-8; 12 – C3b; 13 – Neutrophil; 14 – IL-4; 15 – IgE; 16 – IgG1; 17 – DC; 18 – CD40; 19 – CD40L; 20 – DC licensing; 21 – Tc activation; 22 – B cell activation; 23 – TGF-β; 24 – Th17; 25 – Environment; 26 – TNFa; 27 – IL1b; 28 – IL-6; 29 – IL-10; 30 – IL-17D; 31 – Il-18; 32 – PAI-1; 33 – Heptoglobin; 34 – Serum Amyloid A; 35 – α1-Acid glycoprotein; 36 – 23p3; 37 – CRP; 38 – Adiponectin; 39 – NGF; 40 – MCP-1; 41 – IL1; 42 – IL-2; 43 – NO; 44 – IL-12; 45 – Myeloperoxidase; 46 – CD4+T; 47 – IL-17; 48 – Defensins; 49 – Neutrophil elastase; 50 – Bactericidal/BPI; 51 – Cathepsin; 52 – Lactoferrin; 53 – Gelatinase.

The relations (edges) must be considered as a simple evident interaction, relation, influence, response, activation. Here the network is a graph. A graph is an ordered pair $G = (V, E)$ in which *V* is a set of vertices and *E* is a subset of *V* composed by edges. The graph obtained by the above stated method is connected. This means that given any pair of vertices A and B of a graph *G*, there is always at least one directed path between them – a set of directed edges from A to B or from B to A. This condition is mandatory for the calculations presented below. Furthermore, such condition guarantees that all matter and energy that flows in the network is conserved, which is a very reasonable condition.

Mathematically, we work with the represent: the adjacency matrix of a graph. This matrix is built with the following consideration: if there is a directed edge (arrow) connecting the vertices *i* and *j*, then the value of the adjacency matrix's element a_{ij}equals 1, and otherwise equals 0. In order to calculate the distribution of probabilities, we must define the out-degree of a vertex. Let *x* be a vertex of the graph, the out-degree of *x* is the number of edges that originates in *x*. Mathematically, and using the concept of adjacency matrix, we have: the out-degree of vertex *x* is $k_{x_{out}} = \sum_j a_{ij}$.

All vertices in the network interact dynamically, that is: every vertex generates a signal of increase or decrease of biological activity. To model these dynamics, we used the random walk in the network. The time variable is added to the network, when times increases (discrete), a walker is created in the vertex environment; then if *t* is time, the total number of walkers in the network is $N(t) = t$. The walkers (*i.e.,* particles, information, stimuli, activation, etc.) transits in the network from vertex to vertex, one step per walker per unit of time. The amount (discrete) of walkers in vertex *i* in the time *t* is denoted by $\sigma_i(t)$. Ergo, the relative number of walkers – for now on, information – in a vertex *i* is coined as local flux, defined as $f_i(t) = \frac{\sigma_i(t)}{N(t)}$. Naturally, as times evolves, the values of $f_i(t)$ for any *i* vertex in the network changes. If there are *n* vertices in the network, then there will be *n* values of f_i for every time *t*. Since we want to study the general state of the network, we devised a state vector coined as Flux Vector given by $F_{V(G)}(t) = (f_1(t),\ f_2(t),\ f_3(t), \dots, f_{n-1}(t), f_n(t))$.

Thus, for every time *t*, there is a flux vector $F_{V(G)}(t)$. However, we are interest in generating a steady measurement, for this we want to compute the stationary state of the dynamics performed upon the network. The stationary state of the flux vector for a given network is a vector that does not change with the increase of time, denoted by $F_{V(G)}(t \to \infty) = (f_1'(t \to \infty),\ f_2'(t \to \infty),\ f_3'(t \to \infty), \dots, f_{n-1}'(t \to \infty), f_n'(t \to \infty))$. Considering the stationary state $F_{V(G)}(t \to \infty)$. In dynamics, there is three possible states when times increases indefinitely: a) periodic, that is: the vector $F_{V(G)}$ transits within a set of states with a certain period; b) chaotic, that is: the vector $F_{V(G)}$ transits through a set of infinite states, never repeating; c) stationary, there is only one state as times increases.

In order to test these possible options, it is needed to define the transition matrix *T* of a given graph *G*. This matrix is also known as probability matrix because its entries are probabilities given by $p_{ij} = \frac{1}{k_{i_{out}}}$. This matrix has an algebraic interest in our study, since it can be used for model time, algebraically:$T.F_{V(G)}(t) = F_{V(G)}(t+1)$. Every time the transition matrix operates upon $F_{V(G)}(t)$, times goes on in the dynamics of the flux in the network. Equivalently: $T^t.F_{V(G)}(t=0) = F_{V(G)}(t) \Rightarrow T^{t\to\infty}.F_{V(G)}(t=0) = F_{V(G)}(t \to \infty)$. It is possible to compute numerically $T^{t\to\infty}$ as a limit, but we are interested in an exact evaluation of $F_{V(G)}(t \to \infty)$. For this, we must consider the Perron-Frobenius features of the transition matrix *T*. These features allow one to assert that there exists a unique stationary state $F_{V(G)}(t \to \infty)$, and it can be computed exactly by normalizing the eigenvector associated to the major eigenvalue of *T*. It was considering the set $\{\lambda_i\}$ of eigenvalues of *T*. If the matrix *T* met the following criteria, possessing the Perron-Frobenius features: a)$|\lambda_1| \geq |\lambda_2| \geq |\lambda_3| \geq \cdots |\lambda_{n-1}| \geq |\lambda_n|$ and b) $|\lambda_1| = 1$.

Since the graph is connected – due to the conservation of matter and energy in the time –, it also met the Perron-Frobenius features. This means that $F_{V(G)}(t \to \infty)$ can be calculated exactly, with no need for numeric computation, by normalizing the eigenvector associated to the biggest eigenvalue: 1. An initial graph *G* represents the normal functioning of a phenomenon of interest. When a knockout to a given vertex *i* from *G*, generates in this process a knocked-out graph *G'*. Considering that the transition matrix *T* of *G* met the Perron-Frobenius features, then we can compute the stationary state $F_{V(G)}(t \to \infty)$. Since *G'* is derived from *G*, it will be also connected, ergo possessing the Perron-Frobenius features. This means that we can also compute its stationary state $F_{V(G')}(t \to \infty)$. Using both $F_{V(G')}$ and $F_{V(G)}$ one can calculate the distance between such vectors, given by: $D_{G,G'} = F_{V(G)}(t \to \infty) - F_{V(G')}(t \to \infty) = (\Delta f_1, \Delta f_2, \Delta f_3, \dots, \Delta f_{n-1}, \Delta f_n = f_n)$., where $\Delta f_i = \lim_{t\to\infty}[f_i(t) - f_i'(t)]$ for $1 \leq i \leq n$. Naturally, the values of Δf_i can be positive or negative; if it is positive, it means that the activation of the component is locally increase by the knockout (KO); however, if it

is negative, it means that the activation is locally decreased. For each Δf_i, we can compute its relative error, by:

$$\mu_i = \begin{cases} \dfrac{\Delta f_i}{f_i(t \to \infty)}, for\ \Delta f_i > 0 \\ \dfrac{|\Delta f_i|}{f_i'(t \to \infty)}, for\ \Delta f_i < 0. \end{cases}$$

Collecting all relative error, we can average the set of all error and obtain the relative mean error, which is a global measure: $M_{G,G'} = \frac{\sum_{i=1}^{n} \mu_i}{n}$. This measure is an index, that is, ranges from 0 to 1. If $M_{G,G'}$ is close to 0, then the KO was not significant to the normal functioning of the graph *G*. On the other hand, if $M_{G,G'}$ is close to 1, then the KO is truly relevant to the normal functioning of the graph *G*.

The main measures are: the stationary state $F_{V(G')}(t \to \infty)$ due to a particular KO (also known as Flux Profile): it shows how the local fluxes change with particular KO; and the relative mean error $M_{G,G'}$, which indicates how much a local KO can impact globally. Both quantifiers are very steady and can easily be biologically interpreted in a variety of biological phenomena. We performed the knockouts of all 52 vertices in the COVID-19 and obesity network – regardless of the environment, which would result in nonsense -, and the COVID-19 infection network not considering obesity.

RESULTS

There were built two networks with two sets of results concerning the Relative Mean Error (RME). The first network models the COVID-19 and obesity happening together. The second one models only the effects of COVID-19, Network 1 and Network 2, respectively. Table 1 shows the values of RME and its deviations for both networks.

Table 1. Summarization of relative mean errors (RME) and its deviations to Network 1 and Network 2. The values are decreasing for both cases.

Immunological Agent (Network 1)	RME (Network 1)	Deviation	Immunological Agent	RME (Network 2)	Deviation
Infected Host Cell	0.9010	±0.1870	COVID	1.0000	±0.0000
COVID	0.8645	±0.2407	Infected Host	0.8289	±0.2618
CD40L	0.8559	±0.2752	CD40L	0.8151	±0.3131
IL-17	0.8260	±0.3265	IL-17	0.7817	±0.3457
CD40	0.7929	±0.3227	CD40	0.7807	±0.3214
AR	0.7857	±0.2586	DC	0.7642	±0.3238
Adipocyte	0.7644	±0.2918	Neutrophil	0.6932	±0.3346
AL	0.7634	±0.3008	NK Cell	0.6878	±0.2731
Th17	0.7540	±0.3183	AL	0.6819	±0.3053
Neutrophil	0.7509	±0.3309	IL-4	0.6627	±0.3477
IL-4	0.7304	±0.3565	AR	0.6505	±0.2886
Macrophage	0.7286	±0.2828	IFNα	0.6493	±0.2915
IFN-γ	0.7156	±0.3044	IFNβ	0.6493	±0.2915
NK Cell	0.6875	±0.3197	IFNγ	0.6289	±0.3081
DC	0.6807	±0.3469	Th17	0.6214	±0.3273
IL-8	0.6371	±0.2650	IL-8	0.6099	±0.2586
TGF-β	0.6369	±0.3371	C3b	0.5945	±0.3215
IFNα	0.6351	±0.2870	Tc activation	0.5796	±0.2735
Tc activation	0.6351	±0.3072	B cell activation	0.5796	±0.2735
B cell activation	0.6351	±0.3072	DC licensing	0.5736	±0.2678
DC licensing	0.6351	±0.3072	Macrophage	0.5494	±0.3168
IFNβ	0.6351	±0.2871	IgE	0.5370	±0.3471
IL-1	0.6167	±0.3786	IgG1	0.5370	±0.3471
IgE	0.5948	±0.3631	TGF-β	0.5094	±0.3286
IgG1	0.5842	±0.3592	NO	0.5049	±0.4036
C3b	0.5673	±0.3508	IL-2	0.4967	±0.3751
IL-18	0.5420	±0.3314	Defensins	0.4948	±0.4204
Heptoglobin	0.5203	±0.3767	Neutrophil	0.4919	±0.4173
Serum amyloid A	0.5203	±0.3767	Bactericidal/BPI	0.4918	±0.4172
PAI-1	0.5163	±0.3749	Cathepsin	0.4918	±0.4172
23p3	0.5138	±0.3753	Lactoferrin	0.4918	±0.4172
Adiponectin	0.5130	±0.3747	Gelatinases	0.4918	±0.4172
NGF	0.5130	±0.3747	IL-12	0.4848	±0.3744
MCP-1	0.5130	±0.3747	IL-18	0.4827	±0.3514
CRP	0.5128	±0.3745	TNFα	0.4648	±0.4119
a1-Acid glycoprotein	0.5128	±0.3746	IL-6	0.4594	±0.4141
IL-17D	0.4291	±0.3879	Myeloperoxidase	0.4555	±0.4165
NO	0.4246	±0.3564	IL-1	0.4505	±0.3752
IL-1b	0.4245	±0.3895	IL-10	0.4222	±0.3294
CD4*T	0.4240	±0.3667	CD4*T	0.3939	±0.3923
IL-12	0.4162	±0.3039	Adipocyte	0.0000	±0.0000
Myeloperoxidase	0.4132	±0.3708	Heptoglobin	0.0000	±0.0000
IL-2	0.4052	±0.3187	Serum amyloid A	0.0000	±0.0000
Defensins	0.3992	±0.3407	PAI-1	0.0000	±0.0000
Neutrophil elastase	0.3990	±0.3402	23p3	0.0000	±0.0000
Bactericidal/BPI	0.3990	±0.3402	Adiponectin	0.0000	±0.0000
Cathepsin	0.3990	±0.3402	NGF	0.0000	±0.0000
Lactoferrin	0.3990	±0.3402	MCP-1	0.0000	±0.0000
Gelatinases	0.3990	±0.3402	CRP	0.0000	±0.0000
TNFα	0.3965	±0.3501	a1-Acid	0.0000	±0.0000
IL-6	0.3849	±0.3394	IL-17D	0.0000	±0.0000
IL-10	0.2994	±0.3097	IL-1b	0.0000	±0.0000
Environment	0.0000	±0.0000	*Environment*	0.0000	±0.0000

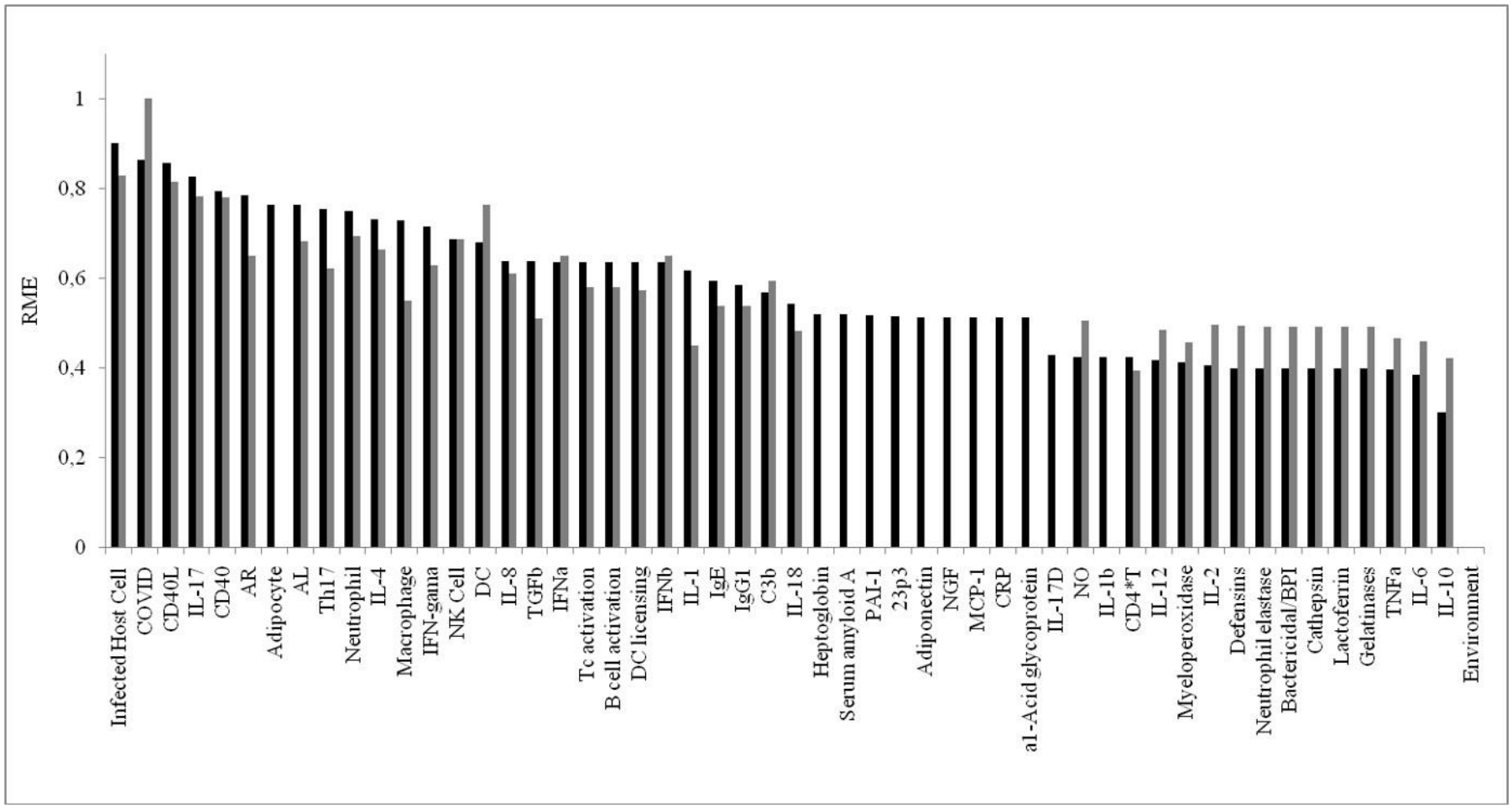

Figure 2. Histogram of the RME of knockouts from Network 1 (black) and Network 2 (grey)

Flux profiles

Here we show the Stationary Flux Vector (Flux Profile) for some knockouts of immunological interest in COVID-19 infections. It was chosen IFNα, IL-6, IL-10, IL-17, and TNFα (Figures 3-7, respectively) as focus for discussion. Other knockouts were made but are not present which are: IFNβ, IFNγ, IL-1, IL2, IL-4, IL-8, and IL-18 (data not shown). It is important to state that these Flux Profiles have as base the Network 1 (COVID-19 and obesity).

IFNα is one of the first response on viral diseases, in our mathematical model it appears as 18th degree of importance, but without these cytokines occur a loss of connection and a suppress of the cascade. The knockout of IFNα is presented at the Figure 3. On the other hand, the Figure 4 shows the importance of the proinflammatory IL-6 in a knockout mathematical network study. One of the principle anti-inflammatory interleukin, IL-10, is being explored on the cytokine storm presented on SARS-COV-19. The Figure 5 shows the IL-10 KO on the COVID-19 obese immune network.

The network developed here, interestingly, shows that IL-17 is the most important secreted substance on the obese plus COVID-19. Figure 6 shows implications of the IL-17KO on the other actors of these disease response. Furthermore, another important immune active cytokine is TNFα (Figure 7) and respective KO made to shows the limiting interaction that occurs without it.

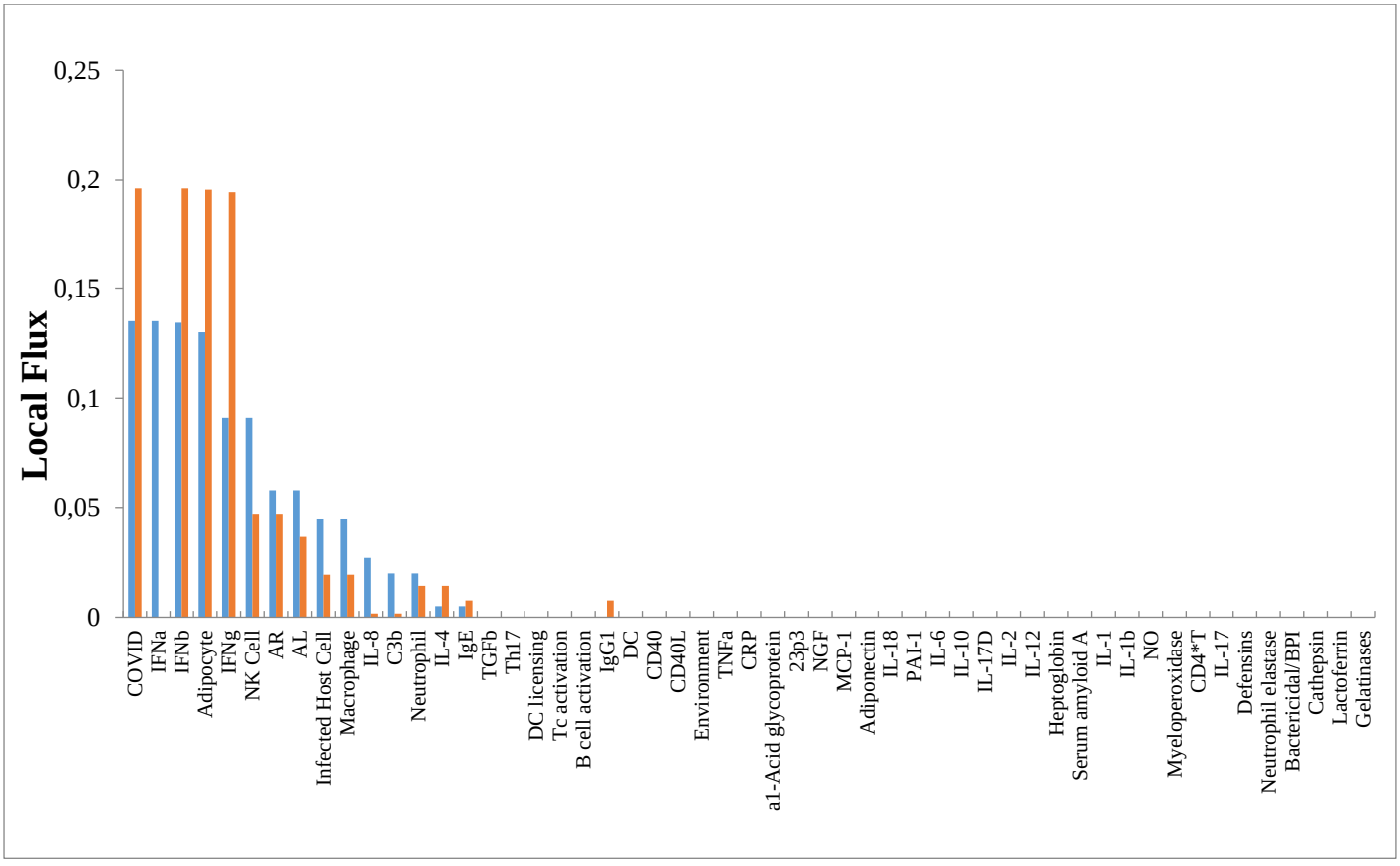

Figure 3. Flux Profile for IFNα knockout and the effect on local fluxes. The blue histogram stands for the Standard Flux (without KO) and the orange histogram stands for the KO flux.

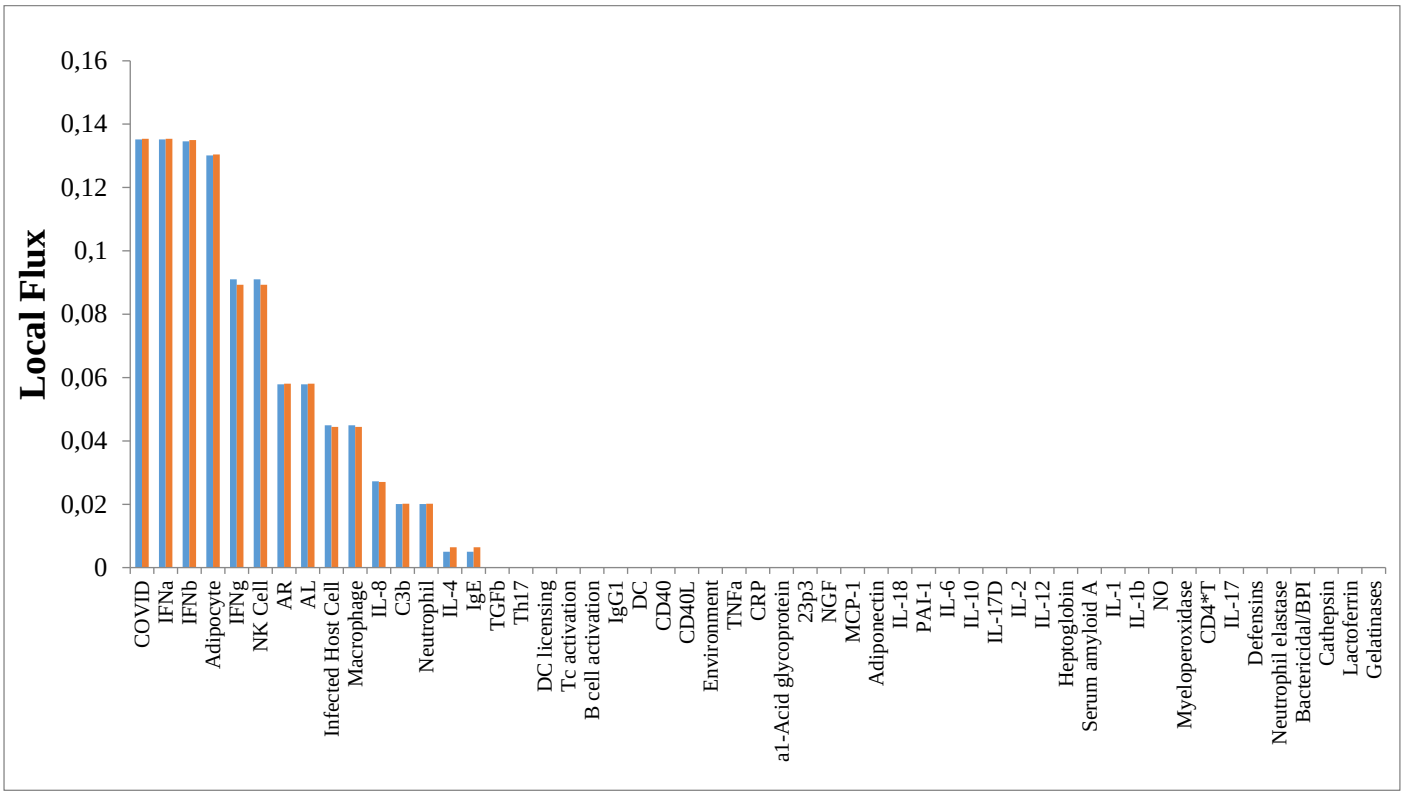

Figure 4. Flux Profile for IL-6 knockout and the effect on local fluxes. The blue histogram stands for the Standard Flux (without KO) and the orange histogram stands for the KO flux.

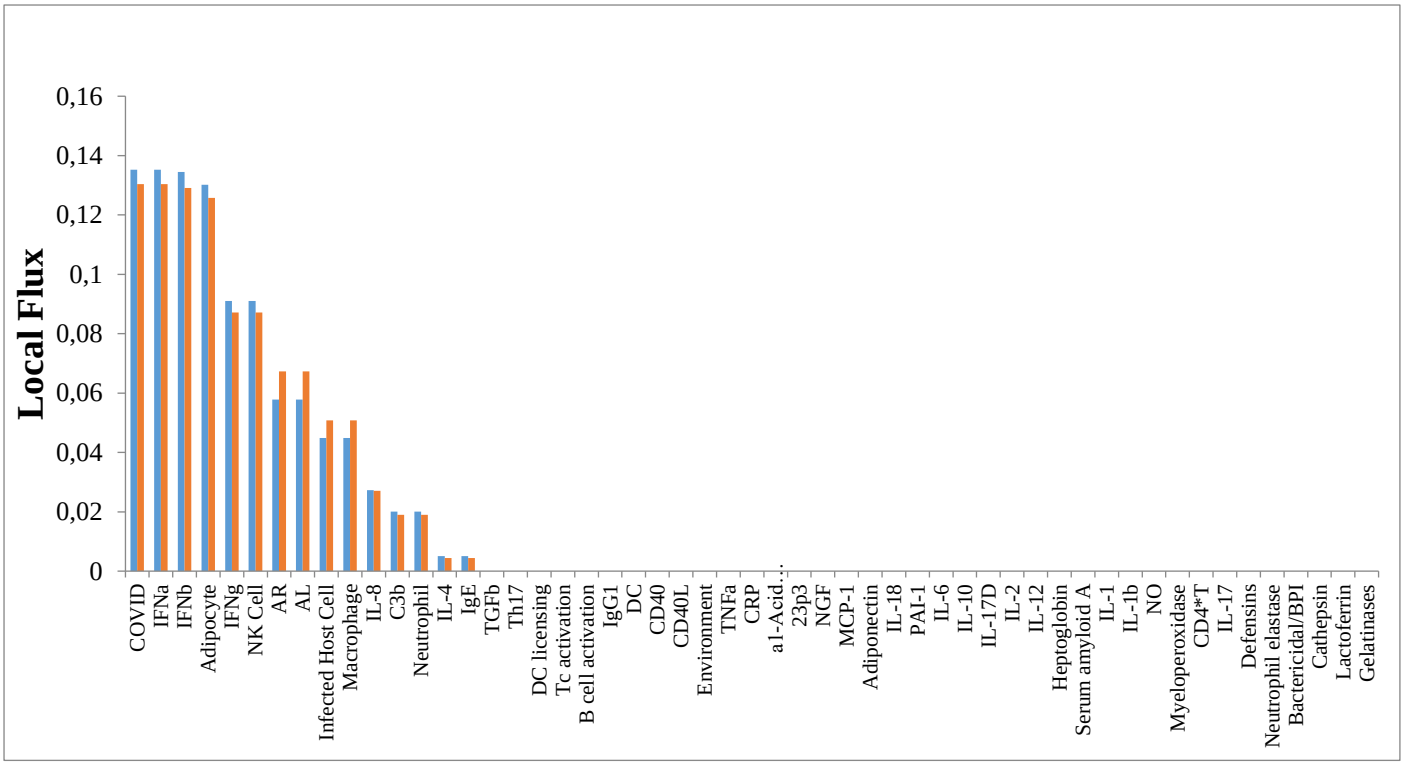

Figure 5. Flux Profile for IL-10 knockout and the effect on local fluxes. The blue histogram stands for the Standard Flux (without KO) and the orange histogram stands for the KO flux.

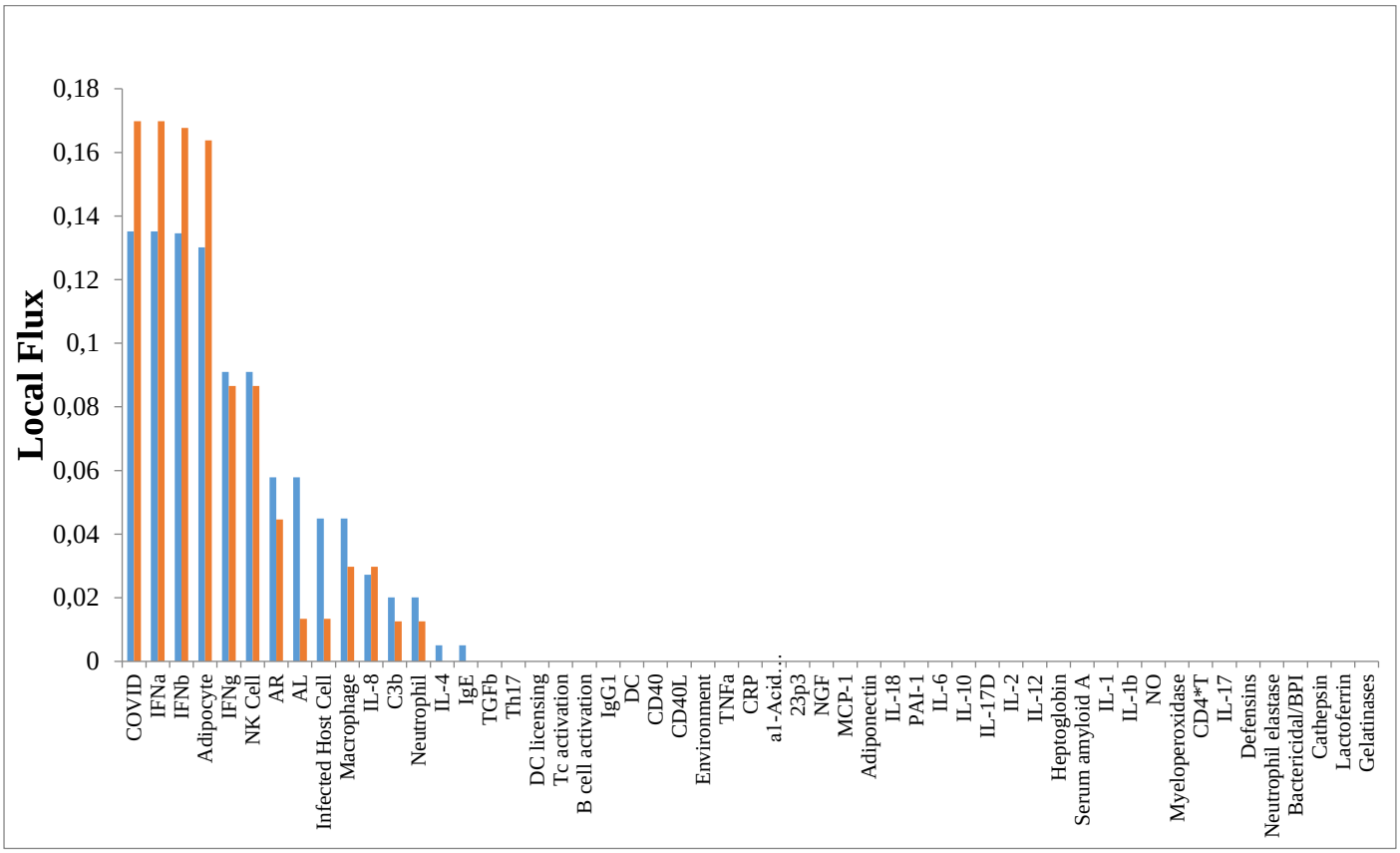

Figure 6. Flux Profile for IL-17 knockout and the effect on local fluxes. The blue histogram stands for the Standard Flux (without KO) and the orange histogram stands for the KO flux.

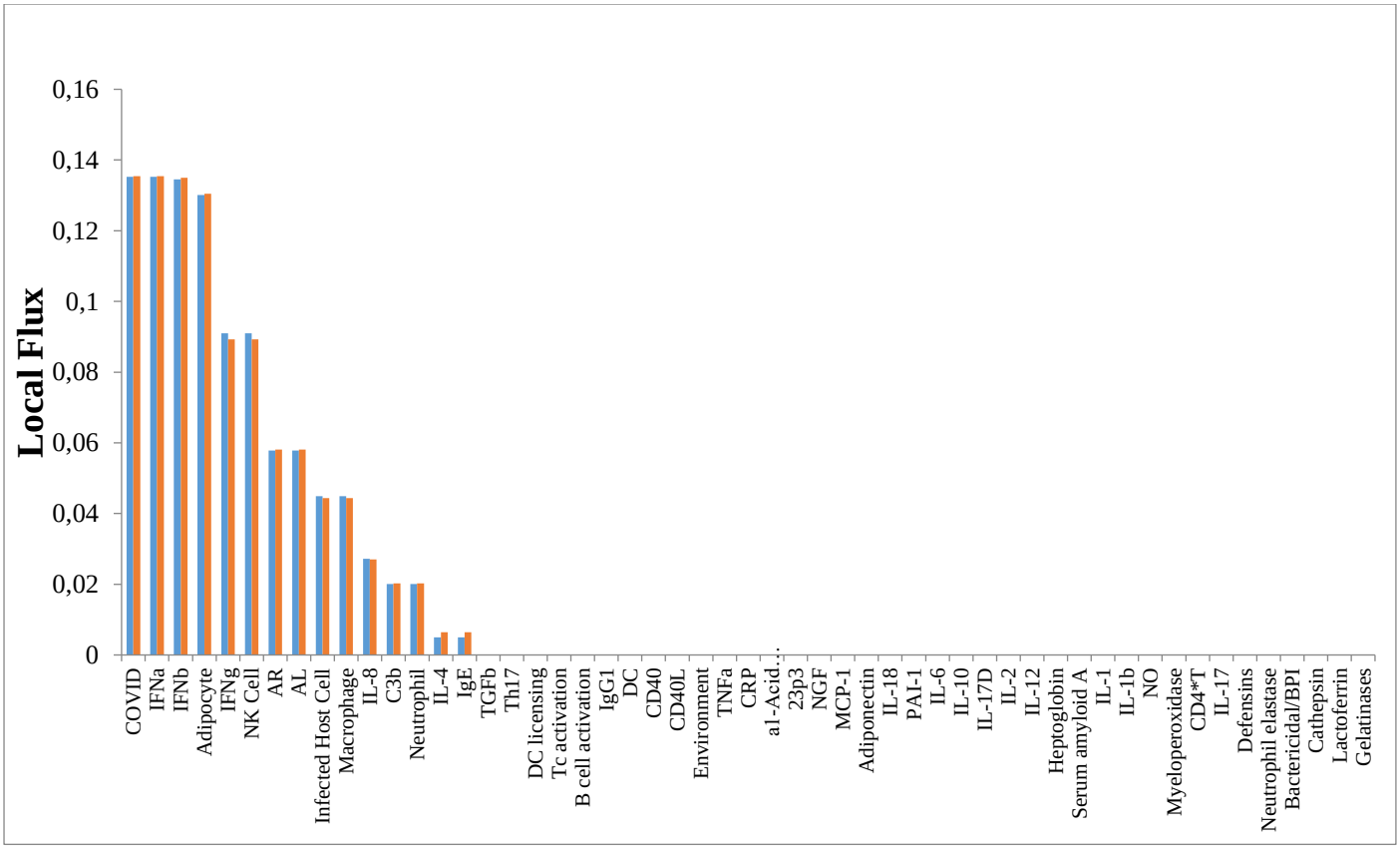

Figure 7. Flux Profile for TNFα knockout and the effect on local fluxes. The blue histogram stands for the Standard Flux (without KO) and the red histogram stands for the KO flux.

DISCUSSION

RME analysis in the complex network shows that infected host cells are more relevant for progression, severity and aggravation of COVID-19 than viral particles itself. In general, viruses are responsible to kill or inactivate host cells and the immune response associated with respective infection will cause a local inflammatory process that elicits an immunopathic disease [19]. Virus-host cell crosslink leads to the first sequence of chemoattractant factors, here, IFNs. Analysis of the KOs shows the importance of these cytokines. In all the results presented (Figures 3-7), these molecules are of greater importance. These substances are related to antiviral state, decreasing cell proliferation, increasing the number of NK and CTL functions.

Another important source of secretion of these cytokines are plasmocytoid DCs [20]. The CD40 present on the surface of the DCs interacts with the CD40L activating T cells. CD40-CD40L binding on DCs interferes with MHC class II-mediated antigen presentation, induces pMHC internalization, and activates T and B cells. T cell activation feeds inflammation by stimulating IFNg, IL-10 and other cytokines. On the other hand, activated B cell secretes IL-10 and TGF-β that induces Th17 recruitment followed by increased secretion of IL-17 [25,27]. In this context, X-linked hyper IgM syndrome and X-linked immunodeficiency with hyper Immunoglobulin M have a large mortality risk by respiratory infection present high alteration in CD40 mutation [28,29]**.** Each syndrome shows increased serum concentrations of IgM.

The evaluation of Figure 2 shows that adipose tissue plays a critical role in this network, given that this tissue constantly supplies TNFα, IL-1, IL-6, IL-8, IL-10, TGF-β, IL-17 and IL-18. Recently, we evaluated the secretion of IL-6 and C-reactive protein in obese patients submitted to removal of the greater omentum, previously and after one year of partial duodenal switch surgery [30]. Both inflammatory markers were significantly decreased, and patients reported improvements in asthma attacks and bronchitis. Here, we suggested that adipose tissue is one of the main actors in the aggravation of the installed inflammatory process. Although mechanisms continue unclear, IL-6 has been characterized as potential biomarker of COVID-19 progression [31]. High levels of IL-6 were correlated with fatality cases in patients with COVID-19 [32]. Moreover, Wang and colleagues showed an intriguing association between significant lung lesions and C-reactive protein levels, in this context, causally linked to disease severity, indicating a possible prognostic test [33].

In patients with COVID-19 in the intensive care unit, increased serum levels of C-reactive protein were frequently followed by elevated number of neutrophils [34. A critical chemokine involved with neutrophil biology is IL-8 [35]. Large amounts of IL-8 were associated with infectious process by SARS-Cov-2 and adipose tissue activity, resulting in neutrophil recruitment and activation. In a study by the University of Leicester, also in a network, but with a focus on proteins and receptors in this disease, they showed a robust response from neutrophils and their important participation [36]. Indeed, circulating IL-8 and IL-6 were associated with lung damage in patients with COVID-19 hallmarked by pneumocyte and endothelial cell infection by SARS-CoV-2 [37].

Regarding to IL-10, serum levels during COVID-19 progression and treatment seem to fluctuate [38]. Correlative analysis between IL-10, IL-6, $CD4^+$ T and $CD8^+$ T cells with pulmonary inflammatory indexes [39]. However, in the course of cytokine storm detected in part of severe patients with COVID-19, levels of IL-10 (together with IL-6 and TNF-α) were significantly associated with lymphopenia and reduced expression of IFN-γ in $CD4^+$ T cells [40]. The involvement of IL-10 in the pathophysiology of COVID-19 in obese patients continues poorly understood.

Another interleukin, and our results, demonstrate an essential role in the severe form of a disease that manifests itself in obese people is IL-17. Our study shows this as the main one mentioned in the developed network. The role of this interleukin has been identified as associated with the risk and prognosis of Acute Respiratory Discomfort Syndrome (ARDS). It is suggested that IL-17 may be a marker for risk prediction and development of ARDS [41]. Interestingly, a recent study [42] reinforced that inhibition of IL-17, which, by the way, is immunologically possible, could be a plausible strategy to prevent acute respiratory distress syndrome (ARDS) in corona virus disease 2019. Part of this statement is due to a 2017 study that evaluated the significant and important increase in IL-17 and Th17 cytokine profile in MERS-CoV [43]. Casillo and colleagues have been proposed that IL-17 should be investigated as high potential therapeutic target to treat COVID-19 related respiratory syndrome [44].

CONCLUSION

This initial study, in a small network, pointed out the importance of chronic inflammation in the obese individual as an important factor in potentiating the disease caused by COVID-19 and, in particular, the need for a clinical study focusing on IL-17. This proved to be a possible therapeutic target to minimize the potential

of the disease in obese people. The expansion of the network and the association with other chronic endemic diseases have already been the subject of new studies.

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