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Individual and meta-immune networks

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Abstract
Networks can be found everywhere—in technology, in nature and in our bodies. In this paper we present how antigen networks can be used as a model to study network interaction and architecture. Utilizing antigen microarray data of the reactivity of hundreds of antibodies of sera of ten mothers and their newborns, we reconstruct networks, either isotype specific (IgM or IgG) or person specific—mothers or newborns—and investigate the network properties. Such an approach makes it possible to decipher fundamental information regarding the personal immune network state and its unique characteristics. In the current paper we demonstrate how we are successful in studying the interaction between two dependent networks, the maternal IgG repertoire and the one of the offspring, using the concept of meta-network provides essential information regarding the biological phenomenon of cross placental transfer. Such an approach is useful in the study of coupled networks in variety of scientific fields.

S Online supplementary data available from stacks.iop.org/PhysBio/10/025003/mmedia

1. Introduction

In recent years, network theory has become one of the central theoretical frameworks that can be applied to the description, analysis and understanding of complex systems and in particular in strongly coupled multi-level complex systems. Complex networks can be found everywhere, in man-made systems and in human social systems, in organic and non-organic matter, in natural and anthropogenic structures as well as in biological systems. Examples include linked molecular or cellular structures, climate networks, communication and infrastructure networks, social and economic networks, gene networks, neuron networks and immune networks. The understanding of the growth, structure, dynamics and functioning of these networks, and their mutual interrelationships, is critical. Most studies have focused on the case of a *single* network that is isolated and does not interact with or depend on other systems. Such situations rarely occur, just as non-interacting systems in statistical physics. In reality, most network systems continuously interact with other networks. Only recently methodologies have been introduced to characterize and investigate interdependent coupled networks [1, 2].

The immune system's role in the body's defense and its constantly evolving daily maintenance of the human body make it an interesting case study of dynamical systems. For example, the adaptive–responsive arm of the immune system stores latent information about body conditions to be used as

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a basis of informed choices for future responses, and in that sense its complexity is comparable to that of the central nerves system. Indeed the antibody response is a classic biological example of a multi-level complex system, with different interacting hierarchical levels that are interdependent. Thus, the challenge is to first describe the topology and structure of the immune system networks, and to then characterize the degree of coupling and interdependence between these networks.

The recently introduced antigen microarray chip [3–7] enables detection in parallel of the patterns of antibodies binding to hundreds of antigens, and thus provides a system-level view of the antibody repertoire. Antibody networks have been studied in the past based on the connectivity between idiotypes and anti-idiotypes—antibodies that bind one another [8–10]. However, in our previous works [11–14], we have called attention to a different network of antibodies, antibodies connected by their reactivity to sets of antigens, according to the antibody isotype, IgM or IgG. In this antigen–reactivity network the nodes represent the antigens spotted on the chip and the links between the nodes represent the relationships between the antibody reactivity calculated for each group of subjects. In other words, an immune network for a given group of subjects corresponds to the network of similarities between antigen reactivity within that group of subjects. In this sense, each type of subject defines its own network; let it be healthy versus sick, males versus females, etc.

In our previous studies [11–14], we presented how the use of advanced analysis methods, originally developed to study various complex networks, can extract meaningful information from a small database that has been extensively studied in the past, and contains IgM and IgG antibody reactivity of the sera of ten healthy mothers and their newborns (umbilical cord samples) that were taken during their full term delivery. The autoantibody reactivities presented in cord blood of the newborns represent the natural immune repertories with which healthy humans begin life and the maternal data (collected at delivery) reflects the development of the repertoires in healthy young adults. For practical reasons, some additional information is included in the supplementary material SI-1, available at http://stacks.iop.org/PhysBio/10/025003/mmedia, includes a detailed description about the antigen microarray technology, SI-2, available at http://stacks.iop.org/PhysBio/10/025003/mmedia, includes a relevant biological overview and SI-3, available at http://stacks.iop.org/PhysBio/10/025003/mmedia, includes a short description of the computational methods that we use.

Our findings supported the known cross placental IgG transfer as we showed that newborn IgG repertoire share similar characteristics with its mother and provided novel evidence that the newborn IgM repertoire is self-produced *in utero* to a similar set of self-molecules. By analyzing the antigen correlations, we found that the maternal repertoire represents a set of individual states, the newborn IgM repertoire represents a common innate state, and the newborn IgG repertoire is a partial reflection of the maternal one. Moreover, the immune state diversity goes hand in hand with the development of modular organization reflected by the formation of antigen cliques, so the intrinsic similarity and network properties of the antigen reactivity levels can be converted into important characteristics of the individual immune state.

Here we make use of the antigen reactivity data as a model study of the interactions between networks and the connection between structural network features and their functional meaning. To this end, we constructed four types of IgG networks, the mothers, the newborns and two meta-networks of mothers and newborns. The meta-networks can be combined either by antigens or by subjects, so for n subjects of the original network and m antigens the meta-antigen network will have the dimensions $2n \times m$ and the meta-subject network will have the dimensions $n \times 2m$. Furthermore, unlike previous works, the current study focuses only the 214 highly reactive antigens (>250) out of the total of 325 antigens that were used on the original dataset.

In terms of biological notion of maternal cross placental IgG passage, the maternal network represents a collection of individual repertoires, the newborn network represents partial reflection of the maternal collection and the meta-networks represent a collection of pairs of repertoires. In this sense, the meta-networks provides an opportunity to study common features of the cross placental passage. Hence, the biological phenomenon provides us with a model to study meta-network and network interactions. In the individual networks (mothers or newborns) there is only minor overlap between the clique antigens, that represent property of the subjects, and the hubs, that represent the property of the antigen network. The meta-subject network also demonstrated similar properties. On the other hand, only in the meta-antigen network there is a significant overlap between the cliques antigens are the major hubs. Consequently, this type of network can be used to identify common features of cross placental IgG transfer and illustrate how network study can be used to study fundamental physiological questions.

2. The antigen cliques

Cliques are subgroups of antigens that exhibit highly correlated reactivities in the different subjects. The concept is illustrated in figure 1, where each subject presents its own unique pattern of reactivity, yet this group of antigens is different between the subjects only in its magnitude. The term clique originates from the network modules in network theory: a clique is a group whose members associate regularly with each other on the basis of common processes and functions. Although more work is needed to show that clique antigen also share common functions, it is important to note that in previous work, gene operons were identified using the same clique identification tool [15].

The identification of antigen clique process involves the following four stages. (1) STD filtering of the antigen–antigen correlation matrix to pinpoint specific sub groups that have significantly higher correlations with the other antigens that belong to the same subgroup, and have high standard deviations with the rest of antigens. (2) Iterative application of the dendrogram clustering algorithm on the STD filtered

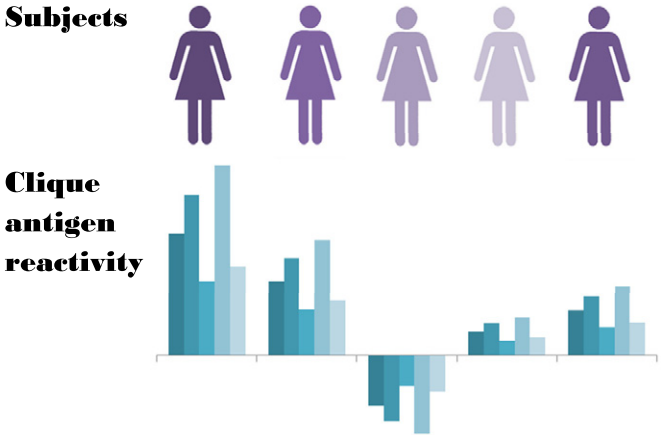

Figure 1. A schematic representative of the concept of antigen cliques. Each clique is composed of antigens that are similar in their pattern but are different in there magnitude, so the personal antigen profiles of those cliques are highly correlated.

antigen subset to select smaller sets of antigens that have Euclidian correlation distances below a certain threshold. This process is repeated three times, gradually decreasing the selection threshold. (3) Searching for additional members using the clique representative reactivity levels. (4) Searching for weaker cliques by removal of the stronger ones through repeating the entire clique identification process on the reduced matrix—the matrix of all antigens that were not selected on the first round. A detailed description of the clique identification tool is given in the supplementary material of [11].

In our previous work [11], we used the clique methodology to characterize the IgM and IgG to study the nature of the immune development in terms of modular organization, and showed that the immune diversity goes hand in hand with the development of modular organization. For the IgM isotype, we showed that the universal congenital IgM network is not organized into cliques (modules or tight clusters) as is the case for the mothers. Thus, the modular organization into autoantibody cliques found in the mothers had been formed during the development of the immune system afterbirth. As for the IgG isotype, we showed that for the IgG isotype that crosses the placenta, the newborns repertoire shows rudimentary modular organization that is only weakly similar to the maternal one. It was concluded that the formation of immune modular organization via the formation of antigen cliques reflects a functional system-level network organization of the immune system. This affords efficient and coordinated performance of immune elements in executing joint tasks. Studying this structure might provide important clues and help understand the formation of functional organization during the development from birth to adulthood, and of the immune system as a whole.

In the current study, we compared the IgG cliques of the three networks: the mothers, the newborns, each networks has 10 subjects and 214 antigens, and 2 meta-networks of mothers and newborns; meta-antigen network of 20 subjects and 214 antigens and meta-subject network of 10 subjects and 428 antigens. As each mother has its own unique repertoire, her offspring will also present a reflection of her repertoire. However, as the IgG cross placental passage is a collective maternal property, it is of interest to study what are the common maternal transferred antigens. The meta-antigen network can thus be used to decipher the features of cross placental transfer as it represents collective reactivities of the maternal-offspring pairs. The meta-subject network can be used to study the personal maternal-offspring link, as it represents ten independent profiles each composed of two states, the innate and the maternal.

Figure 2 presents the clique antigen functional holography (FH) manifolds of the mothers (A), of the newborns (B), of the meta-antigen network (C) and of the meta-subject network (D) (see SI-3, available at http://stacks.iop.org/PhysBio/10/025003/mmedia, for more information about this projection). In short, a dimension reduction is performed on the calculated correlation matrix of the selected clique antigens, and results are projected on the three leading vectors of the PCA [11]. Note that objects that manifest high normalized correlations will be placed in close vicinity in the PCA space.

It is possible to observe that the individual IgG networks exhibit dissimilar clique characteristics; the maternal network has five cliques, where the clique antigens are relatively dispersed, while the newborn networks has four cliques, which seem to appear more condensed. Despite the maternal origin of the congenital repertoire, there are distinct differences in the modularly of the networks, where the maternal network seems to represent a more evolved network. This is in accordance with our previous work [11], using the full set of antigens (including more than 100 low reactivity antigens), where it was shown that there is a weaker modular organization in the newborn network with respect to the maternal one, and that the modularity goes hand in hand with evolution, from the innate state to a mature adult state of the mothers. It is noteworthy, that the maternal transfer of IgG is not sufficient to transfer the maternal modular organization, which could imply that this organization evolves through immune development.

The bottom panel of figure 2 presents the meta-antigen (*C*) and the meta-subject (*D*) networks. It is clear that there is a distinct difference in the topology of the two networks, and the meta-antigen is dominated by a large highly correlated clique with two smaller cliques, where the meta-subject network is characterized by five cliques that are more dispersed. In order to conclude about the functional role of the cliques, we made use of the dependence network analysis (see section 4).

3. Correlation-based antigen selection

Proper antigen selection can be used to address biological questions, such as what is the subset of antigens that has a certain property detected in the subject correlations: for exmaple, the subset of antigens that make the maternal reprtoires more similar (dissmilar), as illustrated in figure 3. This tool is very useful in deciphering biological propeties embeded in the data.

In order to identify subsets of antigens that have common features and may also have biological relevance, we searched the antigen–antigen correlation matrices for antigens that fulfil

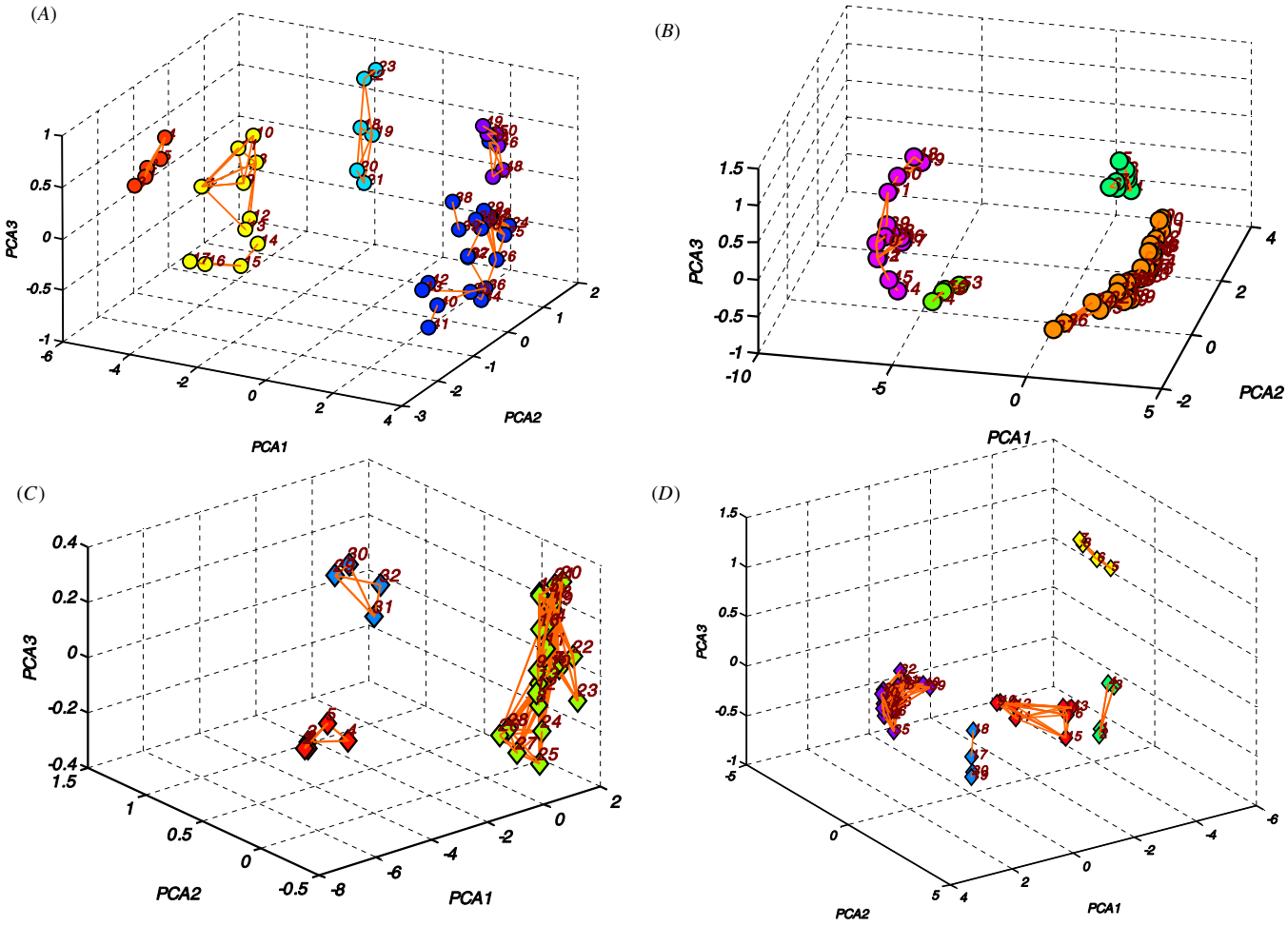

Figure 2. FH manifold antigen cliques of mothers IgG (*A*) and of their newborns (*B*) and of meta-antigen (*C*) and meta-subject (*D*) networks. In the individual networks (*A* and *B*) the nodes are shown as spheres and in the meta-networks the nodes are shown as diamonds, each clique is colored differently. Note the different structural characteristics of each of the networks.

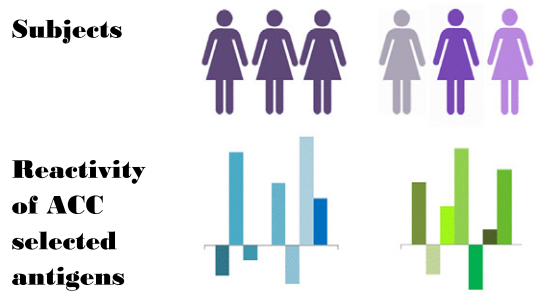

Figure 3. A schematic representative of the concept of ACC approach. The goal is to identify subsets of antigens that contribute to the similarity (left) or the dissimilarity (right) of personal antigen profiles by comparison of their correlation values.

certain criteria. Next, we re-calculated the subject–subject correlation matrix to test the effect on the personal profiling. This procedure has been termed auto cross correlation (ACC) as we test the connection between the self (auto) and the connection (cross) correlation of the subjects.

We used the newborn IgM repertoire to demonstrate how the ACC approach can be used to study populations, as it is a unique state where there is high resemblance of immune repertoires. In order to identify the antigens that dominate the similarity and the antigens that dominate dissimilarity, as small as it is, we used the ACC approach and the results are shown in figure 4 (on the right, subject correlation matrix and on the left, FH manifold). The effect of antigen selection is clearly shown both in the correlation matrices and in the FH projection, where the newborn nodes (blue) are either highly clustered or dispersed in space. We find that 45 antigens dominate the similarity between newborns, and 25 antigens dominate the dissimilarity.

Out of the 45 antigens that dominates the offspring IgM repertoire similarity, 24 are heat shock proteins (HSPs: 4 GroEL peptides, 9 HSP60 peptides, 10 HSP70 peptides and HSP90) where the full antigen list is composed of only 30% HSPs (see table SI-1 available at http://stacks.iop.org/PhysBio/10/025003/mmedia). This is with accordance with known biological knowledge that HSPs are important markers of inflammation and immunological stress, and function as a biomarker of inflammation and stress for the immune system [16, 17] and also with our previous findings about their role as hubs in our dependence network analysis [12]. On the other hand, when testing the dissimilarity

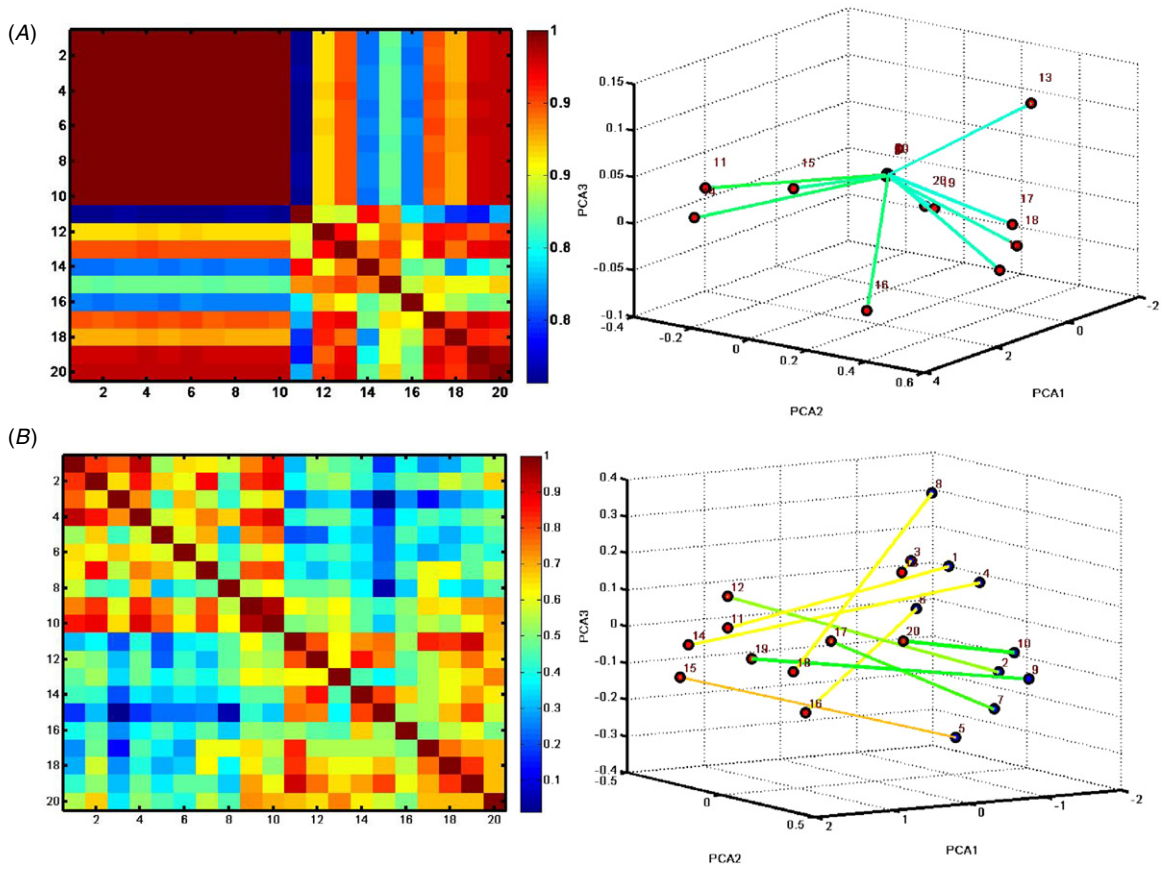

Figure 4. ACC study of the newborn IgM repertoire. Subject-based correlation matrix (right, 1–10 offspring, 11–20 the corresponding mothers) and the resulting FH manifold (left, newborns: red; mothers: blue) using the selected subset of the antigens that govern the similarity (*A*) or the antigens that govern the dissimilarity (*B*). Note the remarkable effect of antigen selection as can be easily detected both in the correlation matrices and FH manifolds.

of the innate IgM repertoires, out of the 25 antigens that dominate it, six are DNA related and six are plasma related. This could be attributed, to the personal genetic origin of the DNA or to indirect connection to the maternal plasma through the placental interface.

In order to study the universal process of cross-placental maternal IgG transfer, we searched for antigens that are commonly different in the foetuses, as compared to the mothers. The results are shown in figure 5 (on the right, subject correlation matrix and on the left, FH manifold). The effect of the antigen selection is clearly shown both in the correlation matrices, where the off-diagonal high correlation value of each offspring to its mother has vanished, and in the FH projection where the offspring nodes (blue) are no longer close to their mothers. Out of the selected 22 antigens, 9 are HSPs and 5 are connecting tissue related. Note that the collection is enriched in HSP antigens that were found to be highly common in the newborn IgM repertoire (see above).

4. Immune dependence networks

The ability of the antigen microarray chip technology to detect global patterns of antibody response to antigens enables the study of the immune system quantitatively using graph and network analysis methods. In our previous works [11–14] we called attention to a different type of immune network, a network of antibodies associated by their reactivity to sets of selected antigens—the antigen-reactivity network. In this immune network, the nodes (circles) represent the antigen reactivity and the links between the nodes (often called edges) represent the relationships between the autoantibody reactivity calculated for each group of subjects. In other words, an immune network for a given group of subjects corresponds to the network of similarities between antigen reactivity within that group of subjects.

Recently, the dependence network methodology, a new method to study relationships of influence, or dependence, by using partial correlations to construct a new type of networks has been introduced [18–20]. Recently, this methodology has been applied to the investigation of the immune system [21], and the investigation of semantic networks [22], validating the applicability of the methodology to different types of complex systems.

The partial (or residual) correlation is a measure of the effect (or contribution) of a given antigen-reactivity, say j, on the correlations between another pair of antigen-reactivity, say i and k. This partial correlation approach enables one to define the hypothetical influence of antigen-reactivity j, SLI(j), as the sum of the influence of that antigen-reactivity j on all other antigen-reactivity i. In this construction of the antigen dependence networks, the nodes represent the antigens

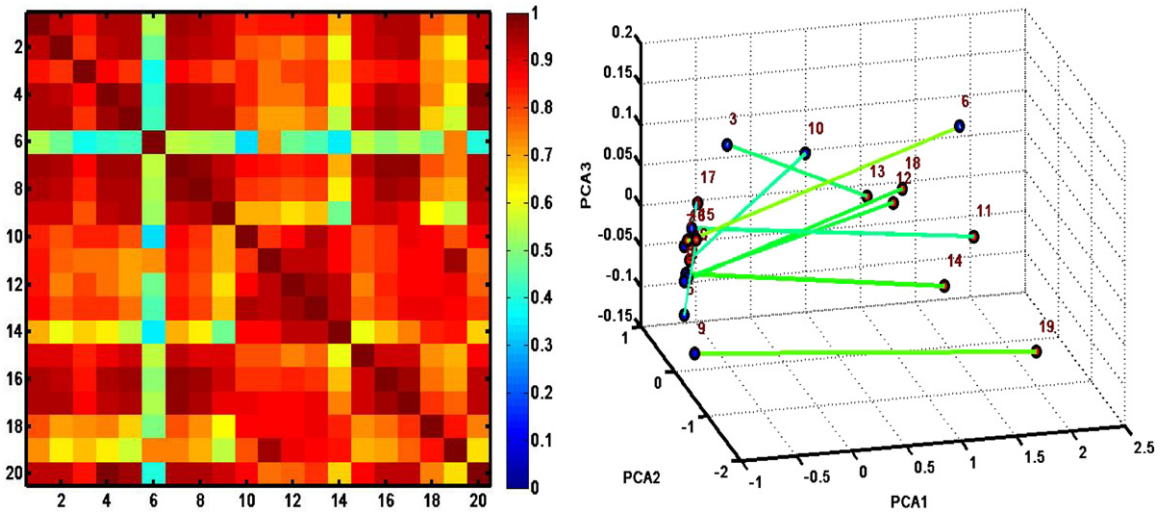

Figure 5. ACC study of the Maternal-offspring IgG repertoire. Subject-based correlation matrix (right, 1–10 offspring, 11–20 the corresponding mothers) and the resulted FH manifold (left, newborns: red; mothers: blue) using the selected subset of the antigens that are commonly different in the offspring as compare with their mothers. Note the remarkable effect of antigen selection where the off-diagonal high correlation value of each mother and her offspring has vanished and the distance of each mother–offspring is high.

Table 1. Spearman correlation score of the antigens SLI ranking values (214 antigens).

Compared networks	Spearman coefficient
Maternal IgG/newborns IgM	0.0741
Maternal IgM/newborns IgG	0.1284
Newborns IgG/IgM	0.1147
Maternal IgM/IgG	0.1558
Maternal IgM/newborns IgM	0.2771
Maternal IgG/newborns IgG	0.5422

spotted on the chip and the arrows between the nodes indicate the directionality of the influence: which antigen-reactivity influences which other antigen-reactivity.

Previous analysis of the system-level influence (SLI) revealed that about 10–15% of the maternal antigen reactivity nodes are hubs [13, 14]; these antigen-reactivities manifest significantly higher driver influences than the other antigen reactivities, as they are evenly spread in the dependence networks. Furthermore, we found that the driver antigen reactivities of the IgG networks are prominently composed of epitopes of HSPs, where the IgM network does not manifest such enrichment. This finding has biological relevance, as HSP60 appears to function as a biomarker of inflammation and stress for the immune system [16, 17], which suits the position of HSPs as hubs or drivers in the maternal and the newborns networks.

The SLI parameter can be used to characterize the network and as a measure of the interaction of networks. In the current study we used the Spearman correlation coefficient as a measure of resemblance of the mothers and newborns network for both IgM and IgG. The results are shown in table 1, the lowest correlation was observed for the mothers IgG and the newborns IgM ($C^s\left(\mathrm{IgG}^{\mathrm{mothers}}, \mathrm{IgM}^{\mathrm{newborn}}\right) = 0.0741$), higher coefficients were observed or the mothers IgM to newborns IgG, and the maternal and newborns repertoires (IgM/IgG) (values). Higher value was found for the IgM repertoire ($C^s\left(\mathrm{IgM}^{\mathrm{mothers}}, \mathrm{IgM}^{\mathrm{newborn}}\right) = 0.2771$) and the highest correlation was found for the IgG repertoire ($C^s\left(\mathrm{IgG}^{\mathrm{mothers}}, \mathrm{IgG}^{\mathrm{newborn}}\right) = 0.5422$). The high correlation between the maternal IgG and the newborns IgG and the low correlation between the maternal IgG and the offspring IgM are in accordance with the known biological phenomenon of cross-placental maternal IgG transfer and self-production foetal IgM repertoire. Also note that there are similar correlation values for the maternal/newborn IgG and the newborns IgM are in accordance with the known IgG cross placental transfer. The analysis shows that dependence network capture known biological behavior. We found the relatively high correlation value of the IgM maternal and newborns repertoire interesting, as it is known that IgM does not cross placenta so resemblance in antibodies repertoires must involve cross placenta antigen transfer.

Next, we calculate the SLI of the antigens in the meta-antigen network, and compare it to that of the antigens in the individual mothers and newborns networks. Figure 6 presents the 20 IgG highest ranked maternal antigens (colored gray), and their marks in the newborns (pink), and in the meta-antigen network (cyan). It is very clear from figure 6 that the meta-antigen scores represent a super set of the maternal and newborns scores.

In the current analysis we constructed the IgG dependence networks (figure 7) for the mothers (*A*), newborns (*B*), meta-antigens (*C*) and meta-subjects (*D*). The appearance coding of figure 2 is kept here and the nodes of the individual networks are shown in circles (basic color gray from mothers and pink for newborns) and in diamonds (basic color orange) for the meta-networks and each the clique nodes are color in the same color scheme of the FH manifold (see figure 2). For clarity, the nodes of each clique are presented sing a different shape. The 20 highest ranked SLI antigens are shown as parallelograms and are of bigger size.

In the maternal network (*A*), the clique antigens are dispersed in the network and there is very low overlap between

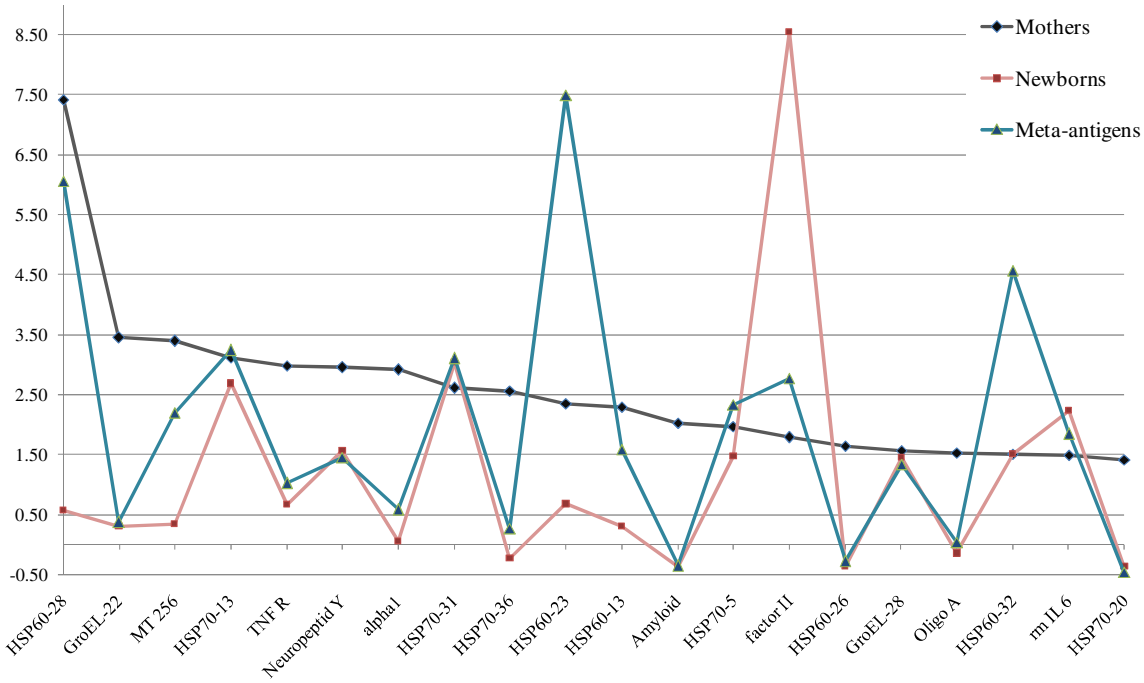

Figure 6. The 20 highest ranked maternal antigens (gray) and the corresponding scores in the newborn network (pink) and meta-antigen network (cyan). Note the meta-antigen behavior reflects the contribution of its primary networks, the mothers and the newborns.

the clique antigens and the 20 highest SLI ranked ones (only two nodes). In the newborn network (*B*), most nodes that belong to same clique are located in proximity to one another (only the 'orange' clique is dispersed), and there is low overlap between the hubs and the clique. Note that the 'pink' clique is exceptional and 40% of the nodes are also hubs. The calculated networks are of first order, so they grasp connection that involves first order intermediate interactions or single body activation, so in case of activation by cascades of interactions or by several immune components, the connection will not appear in the network. As the maternal network represents mature state and the newborn network represents innate state, it seems that the development and the learning of the immune system is involved is differentiation of the network nodes from the naïve congenital state.

The antigen meta-network (figure 7(*C*)) depicts characteristic that it different from the individual networks. 100% (4 out of 4) of the 'blue' clique nodes are also hubs and 52% (12 out of 23) of the 'green' clique nodes are also hubs, so in total 80% of the clique antigens are also raked on the top 20 SLI scores. Thus, it seems that the cross placental IgG passage is first order reaction, so the antigens that are important and shared in all pregnancies are also important hubs in the network. It shows that this unique meta-network both captures and describes correctly the biological phenomenon of maternal antibody transfer.

We further investigated the different aspects of the network, by studying the highest SLI ranked antigens. The top 20 ranked antigens of the mothers, newborns, meta-antigens and meta-subjects are shown in table 2, together with their normalized SLI score. Top 20 ranked antigens that are shared by the mothers and the meta-antigen network are marked in gray, top 20 ranked antigens that are shared by the newborns and the meta-antigen network are marked in pink, and top 20 ranked antigens that are shared by both mothers and newborns are marked in cyan. Out of seven top SLI ranked antigens that are common to both mothers and newborns, six are hub nodes that belong to the 'pink' clique (see figure 7). Investigating the meta-antigen network deciphered that the transport of antibodies that react with Factor II, HSP-70 peptides 13, 31 and 5, Neuropeptide Y and GroEL peptide 28 are shared by all maternal-offspring couples that were tested.

The meta-subject network is of a different kind. It was designed to capture the cross placental passage that modulates the hierarchy of the antigen network. The maternal antigens are marked in black and the newborns antigens are marked in pink. The antigens that appear in both lists are marked in orange. Only 40% of the 20 hubs are both maternal and newborns antigens, which shows that newborn network is not a direct reflection of its mother despite the first order step passage. Figure 8 further demonstrate the different qualities of the meta-subject network. Using the ACC approach, the antigens that dominate the similarity (colored blue) and the dissimilarity (colored red) of the ten united mother–offspring subjects was identified. The most significant hubs are colored green and enlarged. In the insets, the correlation matrices of the meta-subjects with full set of antigens (top), with ACC similar antigens (middle) and with ACC dissimilar antigens (bottom) are shown. It is clear from the dependence network that the ACC selected nodes are not the significant hubs. As this is first order dependence network, it shows that the connections between the mature IgG personal immune repertoires are complex and probably intermediate via non direct associates. Such characteristic behavior was also found in the individual

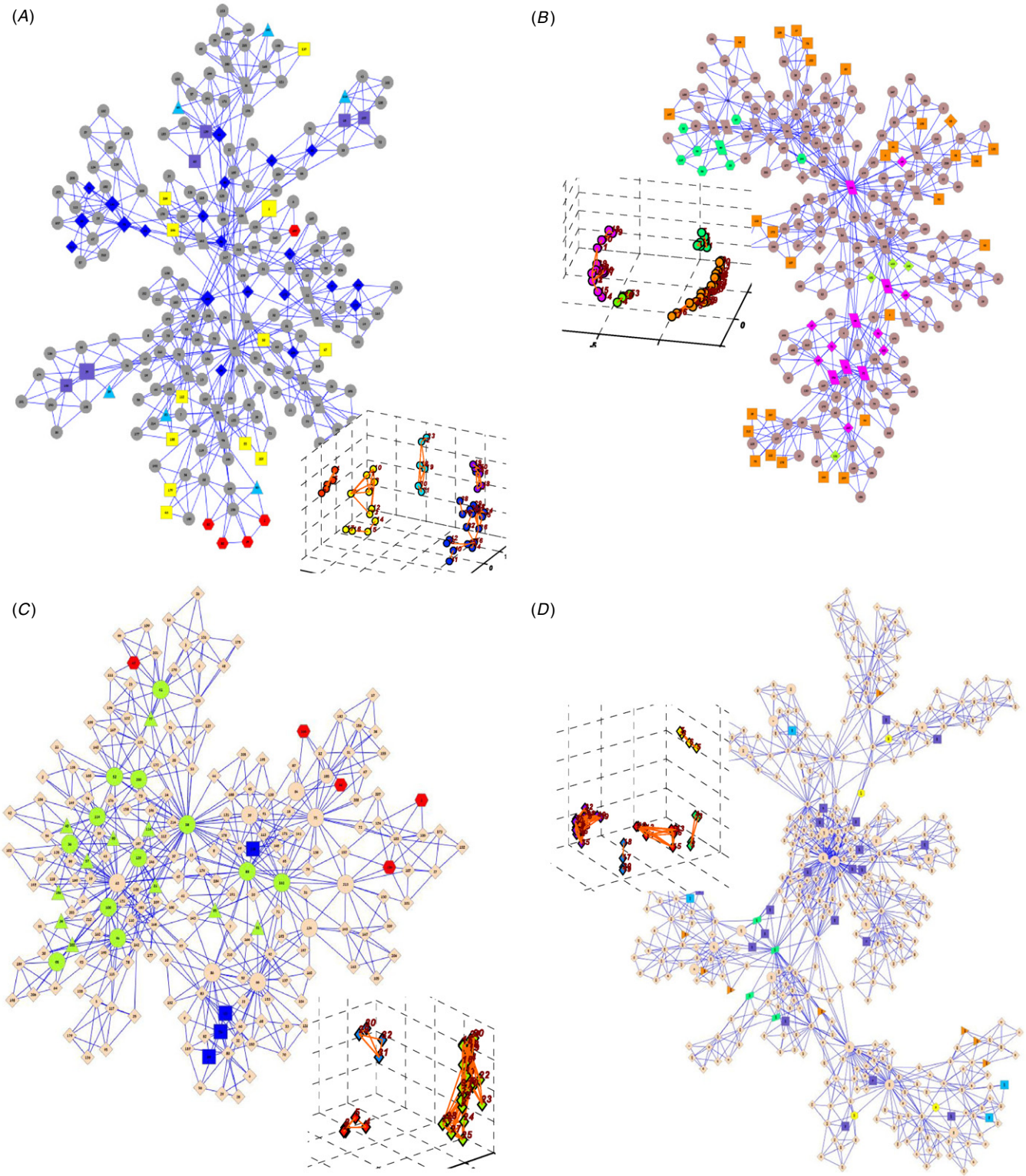

Figure 7. Influential networks of the individual networks (top) of mothers IgG (*A*) and newborns (*B*), the meta-antigen (*C*) and meta-subject (*D*) networks. In each figure, the clique nodes are colored in the coding of figure 2 (in the insets) and have their unique shape. In the individual networks (top) the non-clique nodes are shown in circles and colored gray, mothers and in pink, newborns. In the meta-networks (bottom) the non-clique anodes are shown as diamonds colored light orange. In each network, the nodes of the 20 highest scored SLI antigens are enlarged. Note the different overlap between the clique nodes and the network hubs between the networks.

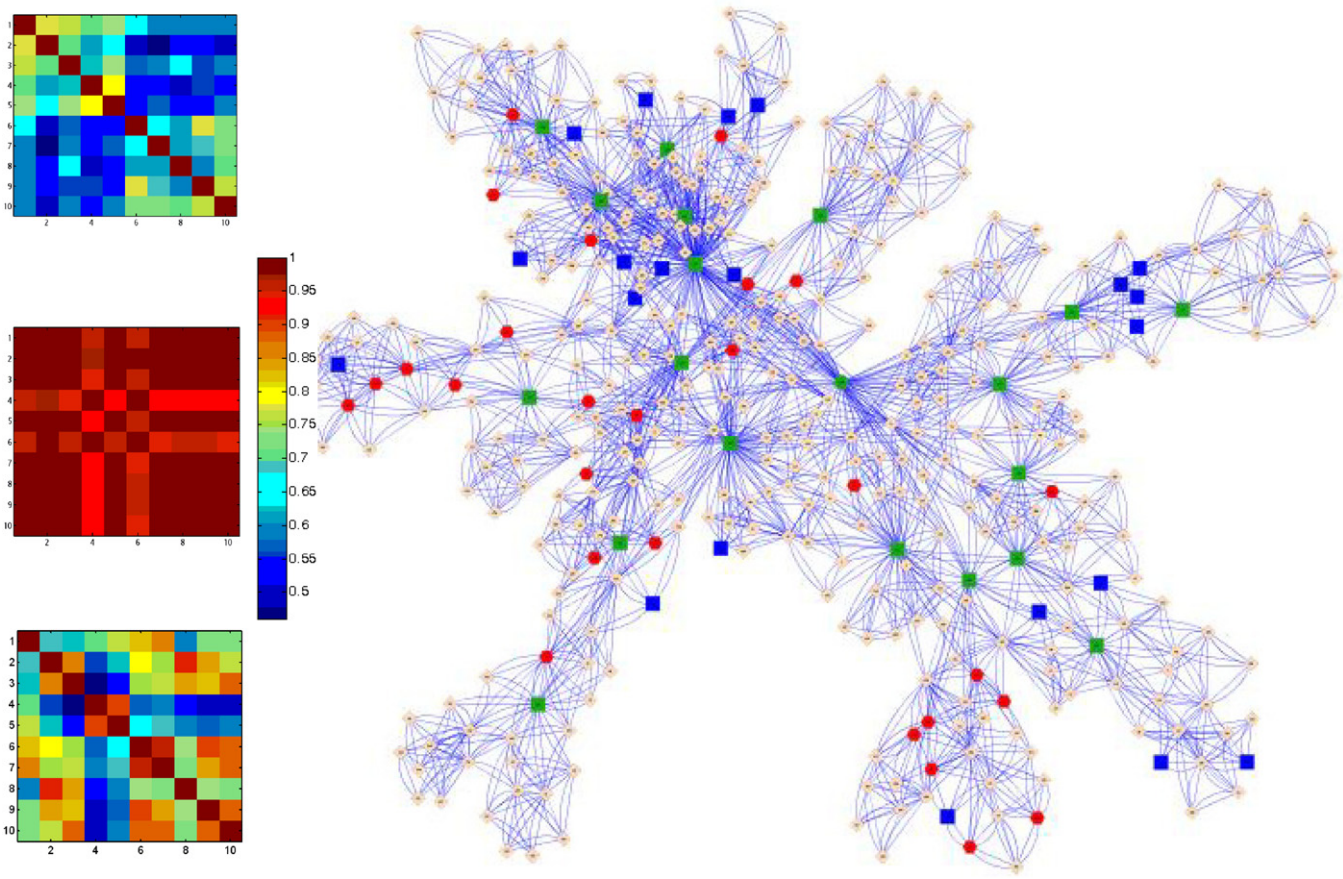

Figure 8. Meta-subject network. The dependence network is shown in the right, the blue squares nodes that are ACC similar, the red hexagonal nodes that are ACC dissimilar and in green and enlarged 20 most significant hubs. For illustration, the corresponding subject correlation matrices of the meta-subjects are show: with full set of antigens (top), with ACC similar antigens (middle) and ACC dissimilar antigens (bottom).

Table 2. 20 highest SLI ranked antigens. Antigens that are shared by maternal and meta-antigen networks are shown in gray, those shared by newborns and meta-antigen networks are shown in gray and those shared by the three networks are shown in cyan. In the meta-subject network, maternal antigens are shown in black and newborn originated antigens are shown in pink, those that appeared from both source are colored orange.

Mothers		Newborns		Meta-antigens		Meta-subjects	
Antigens	SLI	Antigens	SLI	Antigens	SLI	Antigens	SLI
HSP60-28	7.41	Factor II	8.54	HSP60-23	7.49	HDL 39	-0.51
GroEL-22	3.45	Somatostatin	5.85	HSP60-28	6.05	Tubulin	-0.69
MT 256	3.39	HSP60-32	4.20	HSP60-32	4.56	Fibrinogen	-0.74
HSP70-13	3.12	GroEL-18	3.58	HSP70-13	3.24	Alpha 2 microglobulin	-0.75
TNF R	2.98	HSP70-31	3.04	HSP70-31	3.10	HDL 39	-0.77
Neuropeptid Y	2.95	HSP70-13	2.68	Factor II	2.77	Fibrinogen	-0.79
Alpha1	2.91	rm IL 6	2.23	HSP70-9	2.48	KLH	-0.80
HSP70-31	2.61	HSP60-9	2.15	HSP70-5	2.33	Syn beta	-0.80
HSP70-36	2.56	Neuropeptide Y	1.56	MT 256	2.19	Myosin	-0.80
HSP60-23	2.35	HSP70-5	1.47	GroEL-31	1.83	Glyceraldehid 3 phosph	-0.82
HSP60-13	2.28	GroEL-28	1.45	rm IL 6	1.84	Annexin	-0.83
Amyloid	2.02	Vimentin	1.42	RAT MBP	1.79	Ova	-0.83
HSP70-5	1.97	Neurotensin	1.41	HSP70-3	1.66	Vitronectin	-0.84
factor II	1.78	HSP70-4	1.38	HSP60-13	1.58	Tubulin	-0.84
HSP60-26	1.64	Compliment 5	1.25	Neuropeptid Y	1.44	Laminin	-0.84
GroEL-28	1.56	Met BSA	0.99	HSP70-26	1.34	Cytoceratin	-0.85
Oligo A	1.53	HSP70-3	0.97	GroEL-28	1.33	IL 21	-0.85
HSP60-32	1.51	GroEL-24	0.88	GroEL-24	1.27	Annexin	-0.85
rm IL 6	1.48	HDL 39	0.85	Vimentin	1.16	HSP60	-0.85
HSP70-20	1.41	HSP70-22	0.84	TNF R	1.01	EFG	-0.85

networks and it is in accordance with known information regarding the complexity of the adaptive immunity.

5. Summary

Networks are ubiquitous in countless fields of research from electronic circuitry to social networks from transportation systems to biological systems. The use of network science conceptual and methodological approaches is prevalent in a variety of scientific disciplines. Researchers have shown that although networks may superficially be different in their nature, they nevertheless share many global properties; thus, understanding one kind of network can help understand another. However, uncovering the universal characteristics of networks requires the understanding of the basic structural elements present in networks, such as network or motifs (or cliques). Motifs are patterns of interconnections between the nodes in a network, whether neurons, stocks, genes or reactivity of antibodies. Motifs that occur in significantly larger numbers in real networks than in random networks can be used to characterize local features of even the most complex networks.

In our works [11–14] we presented a new approach to investigate antigen microarray data of autoantibody reactivity of IgM and IgG isotypes present in the sera of 10 mothers and their newborns. We were able to show that using advanced network analysis tools, mainly developed in physics, new findings regarding immune development can be uncovered. We find that the immune system at birth is associated with a higher modular organization of the IgG network and more pronounced topological organization of the IgM network. This may indicate a profound and intricate response associated with local and global organizations of the immune network system between the adult and congenital immune states: the IgG networks exhibit a more profound global reorganization while the IgM networks exhibit a more profound local organization. In this paper we studied the interface between the maternal and newborn IgG network using a meta-networks. We were able to show it by constructing the 'right' meta-network, where an important embedded informative interaction can be unveiled.

Our findings of system level modular organization of the immune system are reminiscent of the idiotypic network idea by Jerne [8–10]; yet, we were able to show the immune repertoire, which represents both antibody reactivity to antigens, and can be treated as a network. Indeed more study, based on larger population and with different sets of antigens, is needed in order to provide further support to our findings, but the same approach and its ability to unveil is important, it is expected to be applicable to a wide range of other complex biological networks (e.g. gene networks, protein interaction networks and neural networks), as well as social, financial and man-made networks.

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