

# A bioinformatics and network analysis framework to find novel therapeutics for autoimmunity

Soumya Banerjee<sup>1,2</sup>

<sup>1</sup>University of Oxford, Oxford, United Kingdom;

<sup>2</sup>Ronin Institute, Montclair, USA

E-mail: soumya.banerjee@maths.ox.ac.uk

## Abstract

The immune system protects a host from foreign pathogens. In rare cases, the immune system can attack the cells of the host organism causing autoimmune diseases. We outline a computational framework that combines bioinformatics and network analysis with an emerging targets platform.

The computational framework presented here can be used to find drug targets for autoimmune diseases. It can also be used to find existing drugs that can be repurposed to treat autoimmune diseases based on networks of interactions or similarities between different diseases. Information on which gene regions are associated with the disease (single nucleotide polymorphisms) can be used in gene therapy when that technique becomes viable. Our analysis also revealed immune cell subtypes that are implicated in these diseases. These immune cell subtypes can be selected for immunotherapy experiments. Finally, our analysis also reveals intra-cellular and protein-protein interaction networks and pathways that can be targeted with small molecule inhibitors. The downstream off-target effects of these inhibitors can also be determined from such a network analysis. In summary, our computational framework can be used to find novel therapeutics for autoimmune diseases and potentially even other dysfunctions.

**Keywords** autoimmune diseases, bioinformatics, network analysis, immune system modelling, agent based models, ordinary differential equation models.

## 1 Introduction

The immune system is tasked with protecting a host from external pathogens. It is trained to not recognize self (peptides that are expressed by normal cells in the body of the host). However, in some cases it erroneously recognizes and attacks normal cells in the host. These are called autoimmune diseases.

Insights from bioinformatics coupled with data from emerging curated repositories can lead to novel therapeutics that may ameliorate symptoms of these diseases and help patients lead a normal lifestyle.

We use bioinformatics and network analysis techniques combined with an emerging drug targets platform. We use this approach to show how insights can be derived into potential drug targets of two autoimmune diseases: systemic lupus erythematosus and Sjogren disease. Our work shows the potential of combining computational techniques with emerging repositories to drive insights into the immune system in health and disease.

## 2 Methods

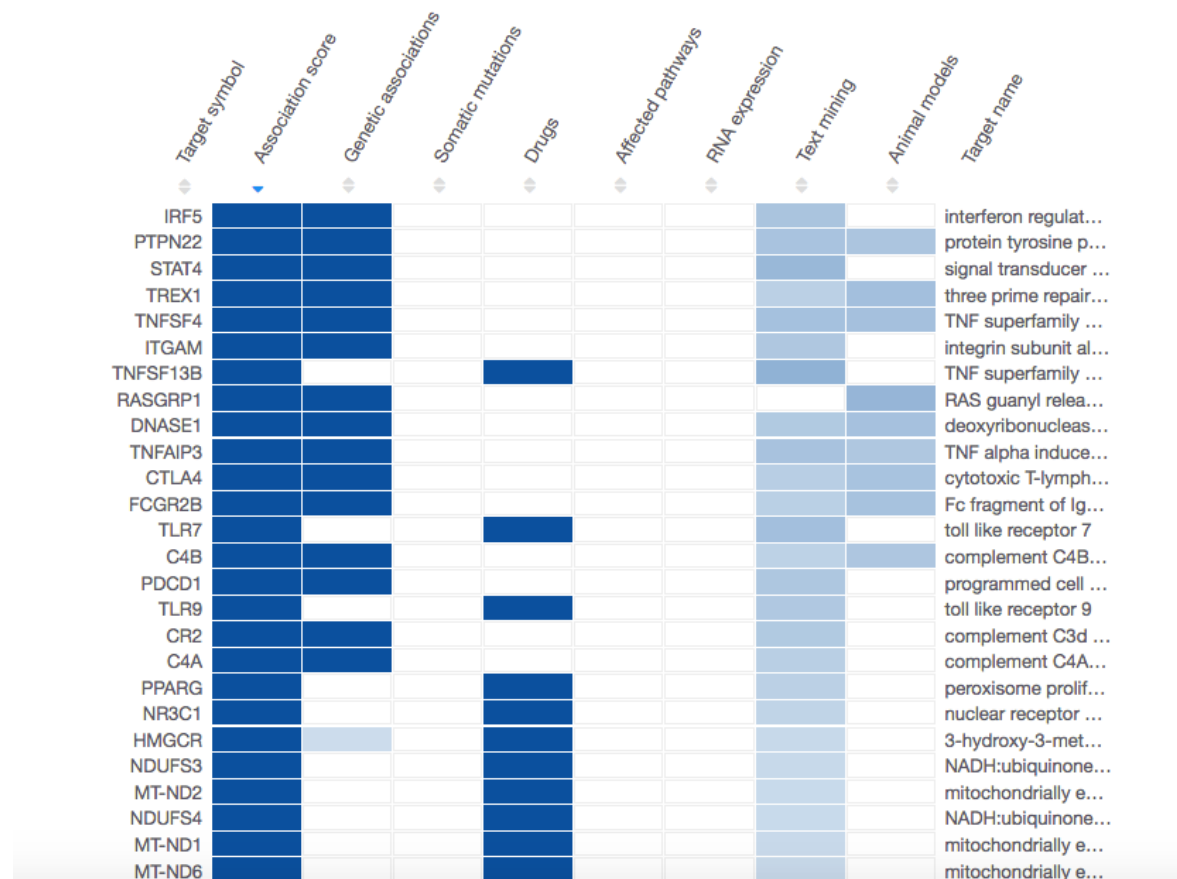
Our approach is to combine bioinformatics and network analysis approach with an emerging platform that has curated information on diseases and their drug targets. We use an emerging platform to quantify targets for an autoimmune disease (<https://www.targetvalidation.org/>) (Koscielny et al., 2017).

Our computational framework combines bioinformatics with network approaches along with a novel repository. Such an approach can enable search for new targets for diseases and insights into mechanisms. We show this approach here for autoimmune diseases. Our code is available for download from a repository ([https://bitbucket.org/neelsoumya/autoimmune\\_targets\\_pipeline](https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline)).

## 3 Results

### 3.1 Top targets associated with systemic lupus erythematosus

Querying the platform revealed that Interferon Regulatory Factor 5 (IRF5) is a top factor involved in systemic lupus erythematosus.



**Fig. 1.** A depiction of the top targets for systemic lupus erythematosus. IRF5 is predicted to be a very important target along with other factors (available from [https://www.targetvalidation.org/disease/EFO\\_0002690/associations](https://www.targetvalidation.org/disease/EFO_0002690/associations) and [https://www.targetvalidation.org/disease/EFO\\_0002690](https://www.targetvalidation.org/disease/EFO_0002690) ).

Some of the known drugs in use or currently in testing for systemic lupus erythematosus are shown in Table 1. Most of the drugs are small molecule inhibitors. A complete list is available in Supplementary Information.

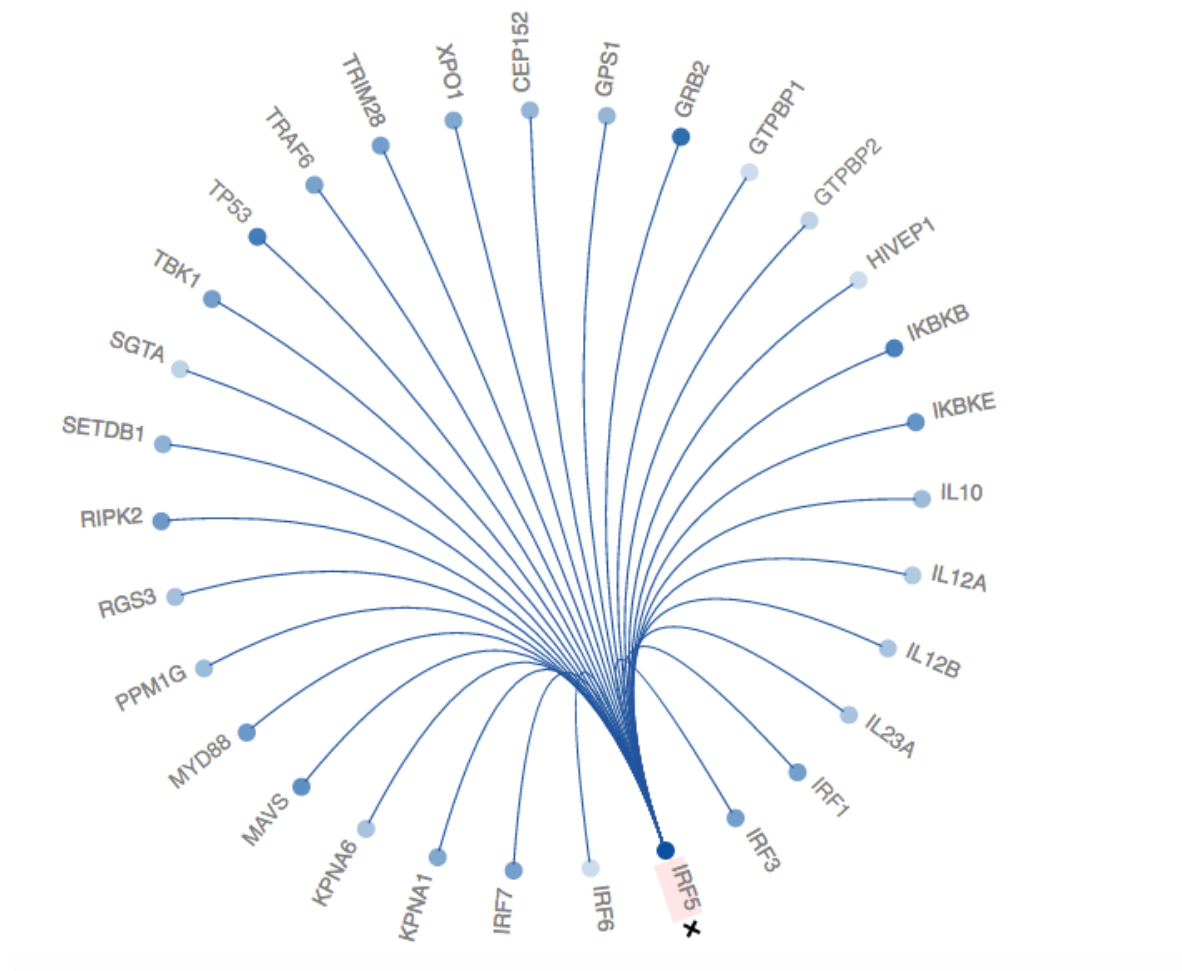
Drug	Type	Mechanism of action
DEXAMETHASONE	N/A	Small molecule
DEXAMETHASONE	N/A	Small molecule
METFORMIN	Recruiting	Small molecule
METFORMIN	Recruiting	Small molecule
PIOGLITAZONE	Completed	Small molecule
DEXAMETHASONE PHOSPHORIC ACID	N/A	Small molecule
PREDNISOLONE	N/A	Small molecule
PREDNISONE	N/A	Small molecule
METFORMIN	Recruiting	Small molecule

**Table 1.** Known drugs in use or testing for systemic lupus erythematosus (top 10 drugs; complete list available in Supplementary Information).

This kind of information can be used to find novel drug targets.

### 3.2 IRF5 interaction network

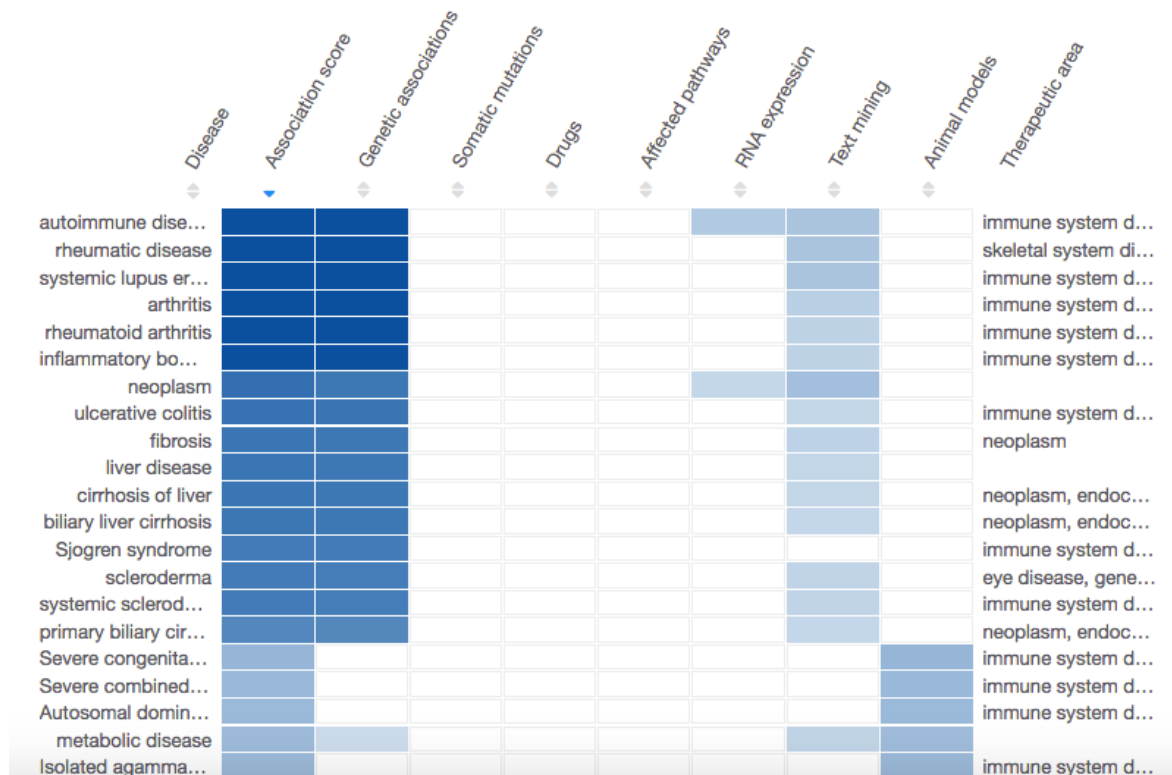
We also constructed the network of interactions between interferon regulatory factor 5 (IRF5) and other factors (Fig. 2).



**Fig. 2.** Network of interactions between Interferon regulatory factor 5 and other factors (available from <https://www.targetvalidation.org/target/ENSG00000128604> ).

This kind of network of interactions with other factors can be used to find drug targets that can influence IRF5.

IRF5 is a very important factor that is also implicated in a host of other autoimmune diseases. We show the association of IRF5 with other diseases like rheumatoid arthritis and inflammatory bowel disease (Fig. 3).

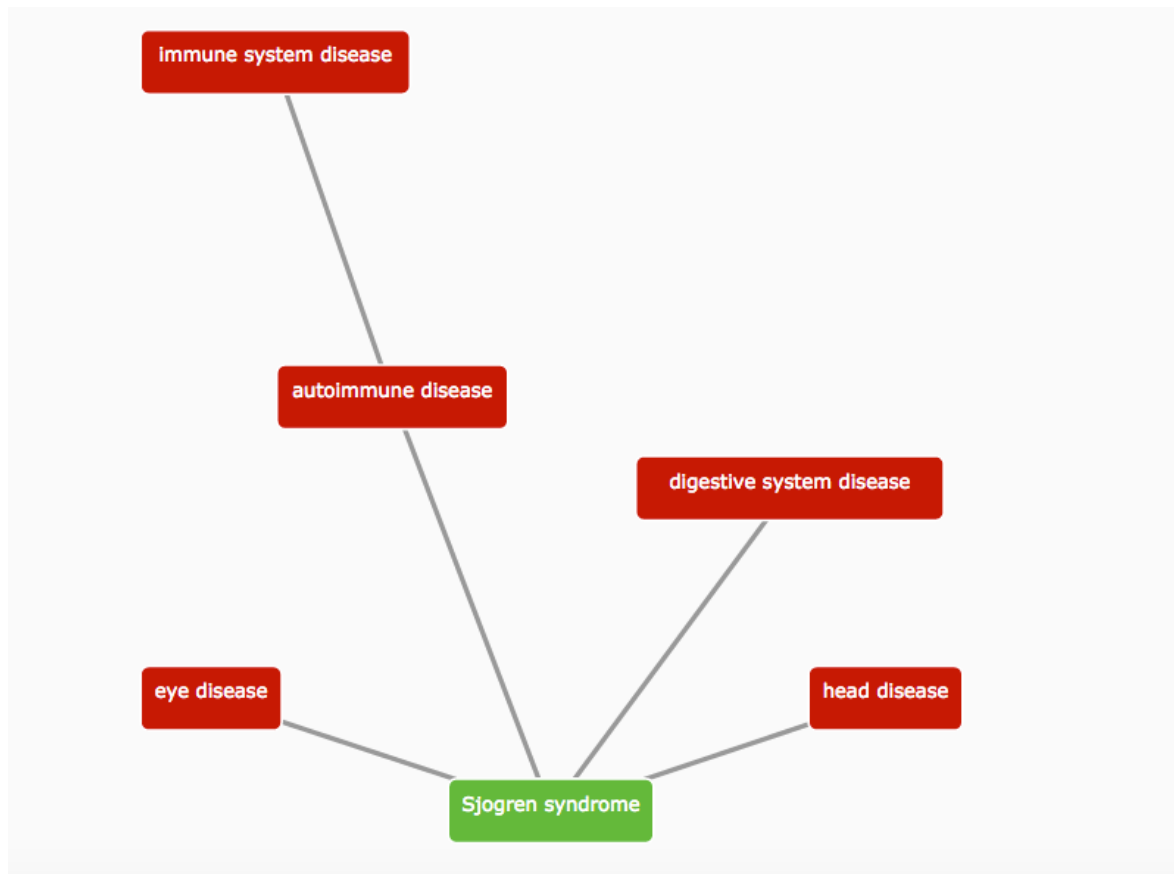


**Fig. 3.** IRF5 is a very important factor that is also implicated in a host of other autoimmune diseases. The diseases are shown in this figure (available from <https://www.targetvalidation.org/target/ENSG00000128604/associations?view=t:table> ).

### 3.3 Interactions with other diseases: Sjogren syndrome

We demonstrate our approach by using another autoimmune disease called Sjogren syndrome.

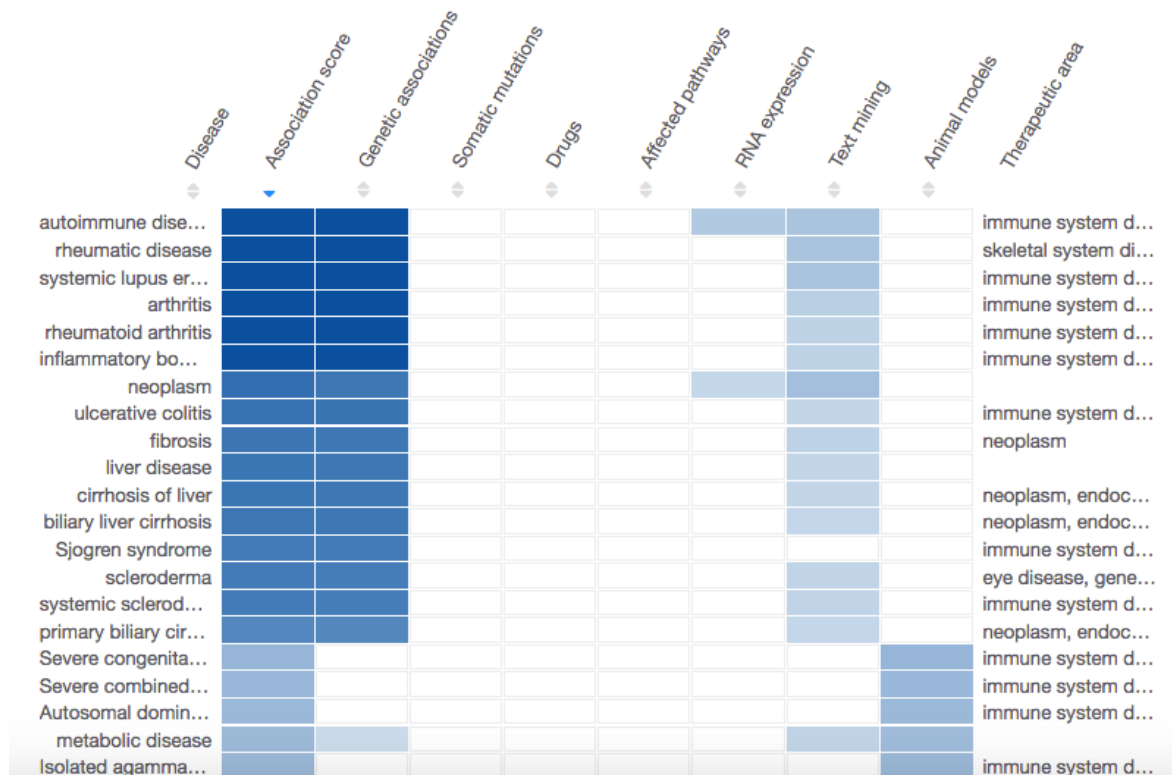
We look at the network of associations between other diseases and Sjogren syndrome (Fig. 4). This kind of information can be used to find existing drugs that can be repurposed to treat this disease.



**Fig. 4.** A network of associations between other diseases and Sjogren syndrome (available from [https://www.targetvalidation.org/disease/EFO\\_0000699](https://www.targetvalidation.org/disease/EFO_0000699) ).

### 3.4 Targets and Associations

The associations of other diseases with Sjogren disorder are shown in Fig. 5.



**Fig. 5.** Associations of Sjogren disorder with other diseases (available from [https://www.targetvalidation.org/disease/EFO\\_0000699/associations](https://www.targetvalidation.org/disease/EFO_0000699/associations) ).

Some of the current drugs that are in use or development for Sjogren syndrome are also shown in Table 2.

Drug	Status	Type	
DEXAMETHASONE	Completed	Small molecule	
HYDROXYCHLOROQUINE	Completed	Small molecule	
HYDROXYCHLOROQUINE	Completed	Small molecule	
BAMINERCEPT	Terminated	Protein	
MYCOPHENOLATE MOFETIL	Enrolling by invitation	Small molecule	
EFALIZUMAB	Terminated	Antibody	
BAMINERCEPT	Terminated	Protein	
BELIMUMAB	Completed	Antibody	
MYCOPHENOLATE MOFETIL	Enrolling by invitation	Small molecule	

**Table 2.** Drugs that are in development or use for Sjogren disorder.



Gene	Consequence Type		
ENSG00000128604 HGNC: IRF5	splice donor variant		
ENSG00000128604 HGNC: IRF5	intron variant		
ENSG00000128604 HGNC: IRF5	intron variant		
ENSG00000128604 HGNC: IRF5	intron variant non coding transcript variant		
ENSG00000128604 HGNC: IRF5	intron variant		
ENSG00000128604 HGNC: IRF5	upstream gene variant		
ENSG00000128604 HGNC: IRF5	upstream gene variant		
ENSG00000128604 HGNC: IRF5	upstream gene variant		
ENSG00000128604 HGNC: IRF5	intron variant NMD transcript variant		

**Table 3.** Genes and transcript consequences for systemic lupus erythematosus (full list available at [http://www.ensembl.org/Homo\\_sapiens/Variation/Mappings?db=core;r=7:128937747-128938747;v=rs2004640;vdb=variation;vf=1430080](http://www.ensembl.org/Homo_sapiens/Variation/Mappings?db=core;r=7:128937747-128938747;v=rs2004640;vdb=variation;vf=1430080) )

Some of the transcripts with tissues where they are likely expressed in are listed in Table 4. A full list is available online (see Supplementary Information; filename: Mappings-Homo\_sapiens\_Variation\_Mappings\_rs2004640.csv).

Gene	Effect size	Tissue
ENSG00000128594	0.002135703	Adipose_Subcutaneous
ENSG00000135245	0.017383528	Adipose_Subcutaneous
ENSG00000240758	0.016198117	Adipose_Subcutaneous
ENSG00000128524	0.019061794	Skin_Sun_Exposed_Lower_leg
ENSG00000128594	-0.118246307	Thyroid
ENSG00000230715	-0.023401133	Adipose_Subcutaneous
ENSG00000243679	0.002803941	Adipose_Subcutaneous
ENSG00000229413	-0.061623932	Adipose_Subcutaneous
ENSG00000271553	-0.070702285	Adipose_Subcutaneous

**Table 4.** Transcripts with tissues where they are likely expressed and effect size (for SNP in rs2004640).

We note that some of the genes (like ENSG00000128594) are associated with thyroid disease, which is observed in patients with systemic lupus erythematosus. Finally, one of the regulatory features (ENSR00000217801) is active in cell lines consisting of many immune system cells (like B cells, natural killer cells and macrophages), and normal cells like those found in the spleen and pancreas (full list available from Supplementary Information; filename: Mappings-Homo\_sapiens\_Variation\_Mappings\_rs2004640\_regulatory.csv). In the future, it may be possible to use therapeutics to specifically target these cells or sites.

## 4 Discussion

The immune system protects the host against foreign pathogens. In rare circumstances, it can harm cells of the host causing autoimmune diseases. We present a computational framework that combines bioinformatics and network analysis approaches with data from a novel platform. Our framework can be used to find novel therapeutic strategies for autoimmune diseases. We show this using two autoimmune diseases: systemic lupus erythematosus and Sjogren disorder.

The computational framework presented here can be used to find drug targets for autoimmune diseases. It can also be used to find existing drugs that can be repurposed to treat autoimmune diseases. For example, Sjogren is associated with other diseases (Fig. 5). Association information of this nature can be used to repurpose existing drugs to treat these diseases.

Information on which gene regions are associated with the disease (single nucleotide polymorphisms in Table 3) can be used in gene therapy when these techniques becomes viable.

Our analysis also reveals intra-cellular and protein-protein interaction networks and pathways that can be targeted with small molecule inhibitors. The downstream off-target effects of these inhibitors can also be determined from such a network analysis (intra-cellular regulatory network for IRF5, Fig. 6).

Our framework also revealed immune cell subtypes and specific sites that are implicated in these diseases (associated with a regulatory feature: ENSR00000217801). These immune cell subtypes can be selected for immunotherapy experiments. In the future, it may also be possible to use therapeutics to specifically target these sites instead of using systemic drugs.

Our approach can be combined with infectious disease models (Banerjee, 2013; Banerjee, 2015; Banerjee and Moses, 2010a; Banerjee et al., 2016). Population level approaches like ordinary differential equations are computationally tractable and can scale up to simulate host pathogen dynamics in large organisms (Banerjee and Moses, 2009). These can also be used to investigate the role of molecular mimicry in autoimmune diseases. Finally, hybrid modelling approaches can also be very useful in modelling these biological systems (Banerjee et al, 2015; Banerjee, 2015b, 2015c).

Our techniques can also be combined with data on auto-antibodies and design specific strategies to increase levels of certain classes of protective auto-reactive (immunoglobulin M) IgM antibodies (Fattal et al., 2010). Our framework can also be used to find classes of T-regulatory cells that have a protective function in autoimmune diseases (Herwijnen et al., 2012). Future work will also investigate linking drug target databases with curated repositories of natural substances such as polyphenol (found in green tea) that have also been known to recruit T-regulatory cells (Wong et al., 2011). This may lead to novel natural compounds that have a protective function in autoimmune diseases. Finally, our framework can be extended to incorporate information on idiotypic networks of antibodies (antibodies that link to other antibodies) that may have a role in autoimmune diseases (Shoenfeld, 2004).

In summary, we present a computational framework for combining bioinformatics with network approaches along with a novel repository can enable us to find new targets for diseases. We show this here for autoimmune diseases. Our code is freely available from a repository ([https://bitbucket.org/neelsoumya/autoimmune\\_targets\\_pipeline](https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline)). Computational techniques like these can shed light on the immune system in disease and help find novel therapeutic strategies.

## Acknowledgment

The author wishes to thank Joyeeta Ghose and Dr. Beverly Kloeppel for fruitful discussions.

## Supplementary Information

A full list of all drugs in use or development and single nucleotide polymorphisms for Sjogren disorder and systemic lupus erythematosus, along with all code is available online ([https://bitbucket.org/neelsoumya/autoimmune\\_targets\\_pipeline](https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline)).

## References

- Gautier Koscielny, Peter An, Denise Carvalho-Silva, Jennifer A. Cham, et al. Open Targets: a platform for therapeutic target identification and validation, *Nucleic Acids Research*, Volume 45, Issue D1, 4 January 2017, Pages D985–D994, <https://doi.org/10.1093/nar/gkw1055>
- Soumya Banerjee and Melanie Moses. 2009. A Hybrid Agent Based and Differential Equation Model of Body Size Effects on Pathogen Replication and Immune System Response. In Timmis, J. (ed.) *The 8th International Conference on Artificial Immune Systems (ICARIS)*, 14–18 (Springer, Lecture Notes in Computer Science, 2009). URL <http://www.springerlink.com/content/b786g874642q2j37/>
- Soumya Banerjee. 2013. Scaling in the immune system, PhD Thesis, University of New Mexico (2013)
- Soumya Banerjee and Melanie Moses. 2010a. Scale Invariance of Immune System Response Rates and Times: Perspectives on Immune System Architecture and Implications for Artificial Immune Systems. *Swarm Intelligence* 4, 301–318 (2010). URL <http://www.springerlink.com/content/w67714j72448633l/>
- Soumya Banerjee, Drew Levin, Melanie Moses, Fred Koster, & Stephanie Forrest. 2011. The Value of Inflammatory Signals in Adaptive Immune Responses. In *Artificial Immune Systems*, 1–14 (Springer, 2011). URL <http://www.springerlink.com/index/U634HJ83W62W5383.pdf>
- Soumya Banerjee and Melanie Moses. 2010b. Modular RADAR: An Immune System Inspired Search and Response Strategy for Distributed Systems. In E. Hart (ed.) *E. Hart et al. (Eds.) Artificial Immune Systems, 9th International Conference, ICARIS 2010, Lecture Notes in Computer Science*, 116–129 (Springer Verlag, Berlin, 2010). URL <http://www.springerlink.com/content/9l062344680u6w76/>
- Melanie Moses & Soumya Banerjee. 2011. Biologically inspired design principles for scalable, robust, adaptive, decentralized search and automated response (RADAR). In *Artificial Life (ALIFE), 2011 IEEE Symposium on*, 30–37 (2011)
- Soumya Banerjee. 2009. An Immune System Inspired Approach to Automated Program Verification, arXiv preprint arXiv:0905.2649, 2009
- Soumya Banerjee and Joshua Hecker. 2015. A Multi-Agent System Approach to Load-Balancing and Resource Allocation for Distributed Computing, arXiv preprint arXiv:1509.06420, 2015

- Soumya Banerjee and Melanie Moses. 2010c. Immune System Inspired Strategies for Distributed Systems. arXiv preprint arXiv:1008.2799, 2010
- Soumya Banerjee, Pascal van Hentenryck and Manuel Cebrian. 2015. Competitive dynamics between criminals and law enforcement explains the super-linear scaling of crime in cities. Palgrave Communications, doi:10.1057/palcomms.2015.22, 2015
- Soumya Banerjee. 2015b. Analysis of a Planetary Scale Scientific Collaboration Dataset Reveals Novel Patterns. arXiv preprint arXiv:1509.07313, 2015
- Soumya Banerjee. 2015c. Optimal strategies for virus propagation. arXiv preprint arXiv: 1512.00844, 2015
- Banerjee, S., Guedj, J., Ribeiro, R. M., Moses, M., & Perelson, A. S. 2016. Estimating biologically relevant parameters under uncertainty for experimental within-host murine West Nile virus infection. *Journal of the Royal Society Interface*, 13(117), 20160130-.<http://doi.org/10.1098/rsif.2016.0130>
- Soumya Banerjee, A Roadmap for a Computational Theory of the Value of Information in Origin of Life Questions, Interdisciplinary Description of Complex Systems, 2016
- Soumya Banerjee, A Biologically Inspired Model of Distributed Online Communication Supporting Efficient Search and Diffusion of Innovation, Interdisciplinary Description of Complex Systems, 2016
- Fattal, I., Shental, N., Mevorach, D., Anaya, J. M., Livneh, A., Langevitz, P., ... Cohen, I. R. (2010). An antibody profile of systemic lupus erythematosus detected by antigen microarray. *Immunology*, 130(3), 337–343. <http://doi.org/10.1111/j.1365-2567.2010.03245.x>
- van Herwijnen, M. J. C., Wieten, L., van der Zee, R., van Kooten, P. J., Wagenaar-Hilbers, J. P., Hoek, A., ... Broere, F. (2012). Regulatory T cells that recognize a ubiquitous stress-inducible self-antigen are long-lived suppressors of autoimmune arthritis. *Proceedings of the National Academy of Sciences of the United States of America*, 109(35), 14134–9. <http://doi.org/10.1073/pnas.1206803109>
- Wong, C. P., Nguyen, L. P., Noh, S. K., Bray, T. M., Bruno, R. S., & Ho, E. (2011). Induction of regulatory T cells by green tea polyphenol EGCG. *Immunology Letters*, 139(1–2), 7–13. <http://doi.org/10.1016/j.imlet.2011.04.009>
- Shoenfeld, Y. (2004). The idiotypic network in autoimmunity: Antibodies that bind antibodies that bind antibodies. *Nature Medicine*, 10(1), 17–18. <http://doi.org/10.1038/nm0104-17>
- Soumya Banerjee. Optimal strategies for virus propagation. arXiv preprint arXiv:1512.00844, 2015
- Soumya Banerjee, Jeremie Guedj, Ruy Ribeiro, Melanie Moses, Alan Perelson (2016). Estimating biologically relevant parameters under uncertainty for experimental within-host murine West Nile virus infection. *Journal of the Royal Society Interface*, 13(117), 20160130-. <http://doi.org/10.1098/rsif.2016.0130>