

Bioinformatics up to Date

(Bioinformatics Infrastructure Facility, Biotechnology Division)
North-East Institute of Science & Technology
Jorhat -785006, Assam
(<http://www.rrljorhat.res.in/biotechnology.html>)



Inside.....

About us	1
Cover story	1
softwares/tools	2
Bioserver/softwares/tools	2
Bioinfo. Animation	3
Upcoming Events	3
Molecule of the month	4
Contact Us	4

Advisor:

Dr Samit Chattopadhyay

Editors:

Dr Y S Devi
Dr R Saikia
Dr SB Wann
Dr H P Deka Baruah

Ms. Esther Jamir

About us

The Bioinformatics Infrastructure Facility (BIF) at Biotechnology division, CSIR NEIST, Jorhat runs under the Biotechnology Information System Network (BTISnet) programme of DBT, Ministry of Science & Technology, and Government of India. The Centre was established on 2nd February, 2008 to promote innovation in Biological research and education through Bioinformatics accomplishment. The main goal is to facilitate and expose students and researchers from different academic institutions of North East India in Bioinformatics. The center conduct training and workshops for enlightening the use of bioinformatics applications in biological research and development. The Centre has access to global information through 24 hour high speed internet facility, and also e-journal facilities with DeLCON, Science Direct etc. To date the Centre has profoundly extended support in R & D work with a great intensity to different biological discipline including medicinal chemistry, computer aided drug design, genomics and proteomic data analysis etc.

MACHINE LEARNING FOR PREDICTING RESPONSES TO TNF INHIBITORS?

Rheumatoid arthritis (RA) is a common inflammatory autoimmune disease and although advances in treatment have occurred over the past decades following biologic therapies, a substantial proportion of patients with RA do not respond adequately to these medications and thus identifying predictors of treatment response is an important clinical and research priority. In a new study, Guan propose a machine learning model that integrates both clinical and omics biomarkers for predicting the response of patients with RA to TNF inhibitors.

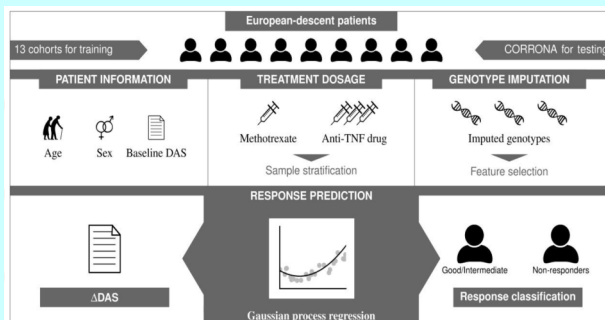


Figure 1: An overview of the drug response prediction model.

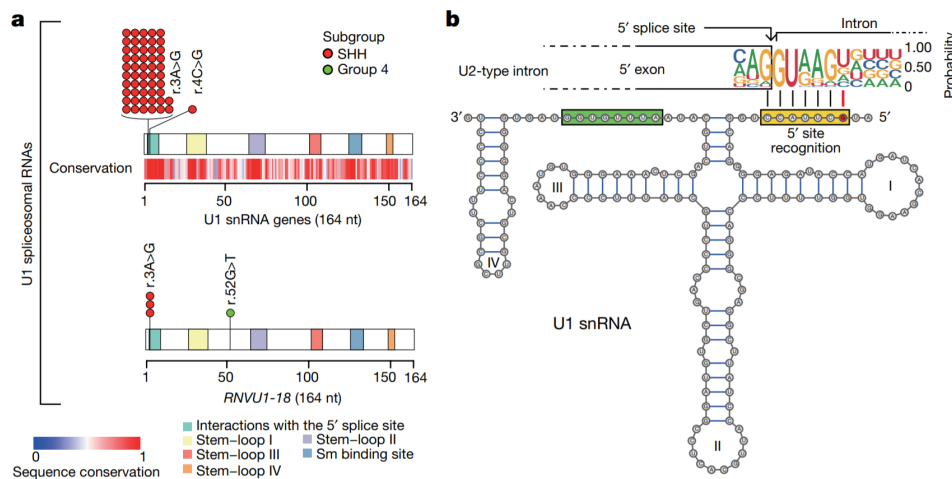
Advances in machine learning have improved constructing models in large and complex health-care datasets by deviating from traditional statistical analyses. These models have the computational capacity to analyze many different variables to generate a powerful predictive model for treatment response. In the model proposed, machine learning models were constructed to predict changes in disease activity scores associated with treatment with TNF inhibitors and used these scores to assign patients to either responder or non-responder groups. Given demographic, baseline disease assessment, treatment, and SNP array data of a patient, their Gaussian process regression model predicts changes in disease activity scores for the patient and classifies the patient into the responder or non-responder group. The model was developed and cross-validated on 1892 patients. It was evaluated on an independent dataset of 680 patients. They examined the effectiveness of the similarity modeling and the contribution of individual features. Gaussian process regression effectively re-mapped the feature space and identified subpopulations that do not respond well to anti-TNF treatments. Genetic SNP biomarkers also show small additional contribution in the prediction on top of the clinical models. The model shows promise in guiding drug selections in clinical practice based on primarily clinical profiles with additional genetic information.

Overall, it is a promising application of machine learning in the development of a model to predict response to TNF. Although the clinical variables have a high predictive power, the potential value of additional omics biomarkers should not be underestimated, as such biomarkers might substantially increase the clinical utility of a machine learning-derived predictive model.

Source: Nisha Nair and Anthony G. Wilson. Can machine learning predict responses to TNF inhibitors? Rheumatoid Arthritis, Rheumatology, Nature reviews.
Guan, Y. et al. Machine learning to predict anti-TNF drug responses of rheumatoid arthritis patients by Integrating clinical and genetic markers. Arthritis Rheumatol. <https://doi.org/10.1002/art.41056> (2019)

NEW CANCER-DRIVING MUTATION IN 'DARK MATTER' OF THE CANCER GENOME.

The mutation represents a new potential therapeutic target for several types of cancer including brain, liver and blood cancer. This target could be used to develop novel treatments for patients with diseases. The non-coding DNA of the genome is difficult to study and is often overlooked since it does not code for proteins but by carefully analyzing these regions studies have shown change in one letter of the DNA code that can drive multiple types of cancer.



Researchers have found a new cancer mechanism that we can target to tackle the disease. In cancer, recurrent somatic single-nucleotide variants which are rare in most pediatric cancers are confined largely to protein-coding genes. In this study the research group discovered that the mutation, termed the U1-snRNA mutation, could disrupt normal RNA splicing and thereby alter the transcription of cancer-driving genes. These molecular mechanisms represent new ways to treat cancers carrying the mutation. One of the potential treatment approaches includes repurposing existing drugs, which, by bypassing early drug development stages, could be

Figure 2: Overview of Highly recurrent mutations of the U1 snRNAs in SHH medulloblastoma. a, Illustration of the number and subgroup-specific distribution of somatic mutations in the U1 snRNA genes. b, Secondary structure of the mutant U1 snRNA.

brought into the clinic at an accelerated rate. The U1-snRNA mutation was found in patient tumors with certain subtypes of brain cancer, including nearly all of the studied samples from adult patients with sonic hedgehog medulloblastoma. The mutation was found in samples of chronic lymphocytic leukemia (CLL) leukaemia and carcinoma.

The study reported highly recurrent hotspot mutations of U1 spliceosomal small nuclear RNAs (snRNAs) in about 50% of Sonic hedgehog (SHH) medulloblastomas. These mutations were not present across other subgroups of medulloblastoma, and identified these hotspot mutations in U1 snRNA in A in only <0.1% of 2,442 cancers, across 36 other tumor types. The mutations occur in 97% of adults and 25% of adolescents with SHH medulloblastoma, but are largely absent from SHH medulloblastoma in infants. The U1 snRNA mutations occur in the 5' splice-site binding region, and snRNA-mutant tumors have significantly disrupted RNA splicing and an excess of 5' cryptic splicing events. Alternative splicing mediated by mutant U1 snRNA inactivates tumour-suppressor genes (PTCH1) and activates oncogenes (GLI2 and CCND2), and represents a target for therapy.

These U1 snRNA mutations provide an example of highly recurrent and tissue-specific mutations of a non-protein-coding gene in cancer. Their discovery uncovered an entirely new way to target these cancers that are tremendously difficult to treat and have high mortality rates and that with one 'typo' in the DNA code, the resultant cancers have hundreds of mutant proteins that might be able to target using currently available immunotherapies.

Source: Science News, Materials provided by Ontario Institute for Cancer Research. Suzuki et al, Recurrent non-coding U1-snRNA mutations drive cryptic splicing in Shh medulloblastoma. Nature (2019).

BIOINFORMATICS WORKFLOW/FLOWCHART/ANIMATION

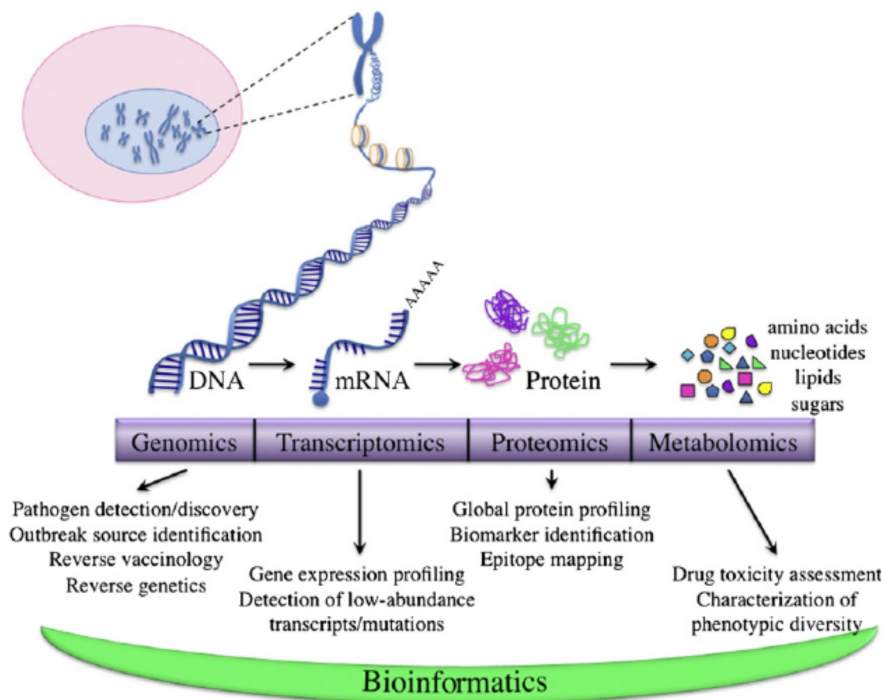


Figure 3: A “top-down” explanation of “omics.” . The above figure illustrates how with the advent of microarray technology and next-generation sequencing, numerous applications have arisen from the field of genomics, including pathogen discovery, epidemiologic advances, and a variety of molecular techniques that allow for precise manipulation of microbial genomes

Source: Fontana *et al*, Translational research in infectious disease: current paradigms and challenges ahead. Translational Research,2012; 159(6):430-453.

UPCOMING EVENT

28-29 March 2020, Hyderabad, India
International conference on Recent Trends in Machine Learning, IOT, Smart Cities & Applications

Submission Deadline	Tuesday 10 Dec 2019	Proceedings indexed by : 
Conference Dates	Mar 28, 2020 - Sep 29, 2019	
Conference Address	Hyderabad, India 	

iccs
INTERNATIONAL CONFERENCE ON COMPUTATIONAL SCIENCE

Amsterdam, The Netherlands | 3-5 June, 2020

Submission Deadline	Friday 13 Dec 2019	Proceedings indexed by : 
Conference Dates	Jun 3, 2020 - Jun 5, 2020	
Conference Address	Amsterdam, Netherlands 	

1. <https://www.iotsmartcon.com/>

2. <https://www.iccs-meeting.org/iccs2020/>

RIBONUCLEOTIDE REDUCTASE

Ribonucleotide reductase creates the building blocks of DNA. DNA and RNA are almost similar in structure, but one small difference has big consequences. A single oxygen atom, that is missing in each DNA nucleotide, distinguishes DNA from RNA. While small, this missing oxygen makes DNA more stable, making it a good molecule for long-term storage of information. On the other hand, RNA is less stable.

Radical Enzyme

The catalytic mechanism of ribonucleotide reductase is interesting because it requires free radicals. While free radicals are usually harmful for our bodies, in ribonucleotide reductase they play an essential role in production of the building blocks of DNA. While ribonucleotide reductase is a highly conserved enzyme across all forms of life, there are many different classes that use different metals to generate these essential free radicals.

Target for Cancer Treatment

Ribonucleotide reductase is an important target for anticancer drugs. One way of stopping the growth of cancer cells is to shut down the enzymes involved in DNA synthesis. The obvious way of inhibiting this enzyme would be to create a molecule that looks like a nucleoside and blocks binding of normal nucleoside diphosphates in the active site. However, because nucleoside analogues are very similar to actual nucleosides used in the cell, they may be incorporated into DNA made by healthy cells as well as cancer cells, which results in bad side effects.

Checks and Balances

Because ribonucleotide reductase is essential for DNA synthesis, it is highly regulated in the cell and only works when necessary. When the concentration of ATP in the cell is high, ATP binds to ribonucleotide reductase as a signal to make more deoxyribonucleotides. This usually happens during cell division, as a lot of new DNA is created at that time. Besides that, ribonucleotide reductase has a separate site that senses which deoxyribonucleotides are required. To prevent the enzyme from making toxic levels of deoxyribonucleotides, dATP binds to the enzyme and shuts it down magnetite crystal.

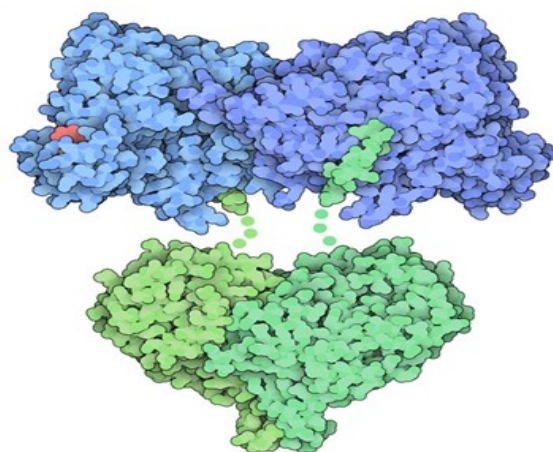


Fig 4: *Escherichia coli* ribonucleotide reductase forms a tetramer with two alpha subunits (blue) and two beta subunits (green). A nucleotide (red) is bound in a regulatory site in this structure.

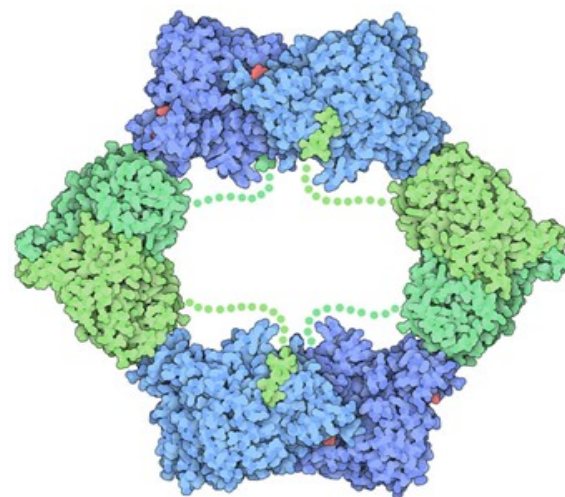


Fig5: Inhibited state of ribonucleotide reductase.

Source: <http://pdb101.rcsb.org/motm/238>

Kindly send us your feedback to

Dr Ratul Saikia
BIF Center, Biotechnology Group, BSTD
CSIR-North East Institute of Science and Technology, Jorhat,
Assam
E-mail: rsaikia19@gmail.com

Dr Yumnam Silla Devi
BIF Center, Biotechnology Group, BSTD
CSIR-North East Institute of Science and Technology, Jorhat,
Assam
E-mail: bio.sillayumnam@gmail.com