BIOGRAPHICAL SKETCH

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NAME: BHANOT, GYAN

eRA COMMONS USER NAME (credential, e.g., agency login): GBHANOT

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
MS University of Baroda, India	BSc	05/1972	Physics, Math, Statistics
IIT Bombay, India	MSc	05/1974	Physics
SUNY Stonybrook	MA	05/1975	Physics
Cornell University	PhD	08/1979	Theoretical Physics
Brookhaven National Laboratory	Post-doc	06/1981	Physics
Institute for Advanced Study, Princeton	Member	06/1984	Natural Sciences
CERN, Geneva, Switzerland	Post-doc	05/1983	Particle Physics
Institute for Theoretical Physics, UCSB	Post-Doc	06/1985	Theoretical Physics
Supercomputer Institute, FSU	Senior Scientist	05/1987	Machine Learning, Big Data
Thinking Machines Corporation	Senior Scientist	05/1994	Parallel Computing Algorithms
IBM Research, Yorktown Heights, NY	Research Staff Member	07/2006	Computational Biology, Computer Algorithms, Statistical Physics

A. Personal Statement

I am a Computational Biologist with research interests in cancer bioinformatics, population genetics and disease association studies. At Rutgers University, I have joint appointments in the Department of Molecular Biology and Biochemistry and the Department of Physics. I am also a Member of the Rutgers Cancer Institute of New Jersey (Rutgers Cancer Institute). I work closely with many physicians and researchers at universities and medical institutions in the USA, Norway, Holland, and India. Trained as a physicist, I have been working on problems in Systems Biology since 2001. As a result of my work at Thinking Machines and IBM Research, I have extensive experience with computational methods in the field of Deep Learning, including the analysis of large datasets, statistical inference methods, parallel programming algorithms, model building and pattern recognition. My research focus is to use machine learning, modeling, simulations, computation and analytical reasoning to understand biological phenomena, using genomic, genetic and phenotypic data. My students and I are working on several projects in cancer bioinformatics, viral evolution, yeast genetics and ribosome biology. The most recent research focus in my group has been on understanding response and resistance to immune checkpoint therapy.

Research Support

M2GEN and ORIEN PI: Ganesan 06/01/2019-05/31/2023
"Chromatin abnormalities and endogenous retrovirus expression as a novel biomarker of response immune checkpoint therapy in low mutation
Role: Co-investigator

KC180159 PI: Ganesan 04/01/2019-3/31/2021
Department of Defense (DoD)
"Endogenous Retrovirus Expression, Chromatin Abnormalities, and Response to Immune Checkpoint Blockade in Clear Cell Renal Cell Cancer"
Role: Co- investigator

B. Positions and Honors

Positions and Employment

2006-present Professor, Department of Molecular Biology and Biochemistry and Department of Physics; Member, Rutgers Cancer Institute of New Jersey
2002-2010 Adjunct Professor, Bioinformatics Program, Boston University Interdisciplinary Programs
2013-present Adjunct Professor, Tata Institute of Fundamental Research, Mumbai, India
2002-present Visiting Professor, Simons Center for Systems Biology, Institute for Advanced Study, Princeton
2014-present Elected General Member of the Aspen Center for Physics
2013 Team leader of AMG team (Bhanot, Biehl, Dayarian, Hormoz) awarded first prize in Sub-challenges 1,2,3 in the sbv- Improver Species Translation Challenge https://www.sbvimprover.com/ at the Symposium in Athens Greece, October 28-31, 2013
2006 Supercomputing Gordon Bell Award for paper titled: 'The BlueGene/L Supercomputer and Quantum Chromodynamics' in the category, "Special accomplishment for innovation in scalable implementation"
2006-present Reviewer for: AACR, Bioinformatics, Biophysics Journal, BMC Bioinformatics, BMC Cancer, BMC Systems Biology, British Journal of Cancer, Cancer Research, Cell Reports, Clinical and Vaccine Immunology, Genome Medicine, Genomics, Human Genetics, IJJCR, ISMB, JCI, JCO-PO, Journal of High Performance Computing, Molecular Oncology, Nucleic Acids Research, PLoS Computational Biology, PLoS One, PLoS Pathogens, PNAS, RECOMB, Science TM, Scientific Reports, SIAM Journal of Scientific Computing, Transactions on Parallel and Distributed Systems

Patents

2009 "Class Network Routing", US 7,587,516 B2, Sept. 8, 2009
2011 "Method and System for Robust Classification Strategy for Cancer Detection from Spectrometry Data", US 7,899,625 B2, March 1, 2011
2008 "Efficient Implementation of a Multi-dimensional Fast-Fourier Transform on a Distributed Memory Multi-Node Computer", US 7,315,877 B2, Jan.1, 2008
2006 Optimizing Layout of an Application on a massively Parallel Supercomputer", US 2006/0101104A1
2008 "Method of Identifying Robust Clustering", US 2008/03

C. Contributions to Science in Biology

1. **Immune Checkpoint Therapy:** Most recently, using TCGA and clinical data, we have identified several mechanisms of response to immune checkpoint therapy: (i) We discovered the existence of a tumor mutational burden threshold, identifiable in clinical assays, that separates likely responders from likely non-responders in eight sold cancers. The likely responders have very distinct mutational signatures and mechanisms of immune activation. (ii) Stomach cancers with a sufficiently high expression of Epstein-Barr-Virus transcripts have evidence of a blocked immune response and upregulation of checkpoint pathway genes and are likely to respond to PD-1 blockade therapy. (iii) In ccRCC, Colon, Head-Neck and ER+/HER2- breast cancer, high expression of the endogenous retrovirus ERV3.2 is a marker of response and associated with histone anomalies4.
    a. Mehnert JM, Panda A, Zhong H, Hirshfield K, Damare S, Lane K, Sokol L, Stein MN, Rodriguez-Rodriquez L, Kaufman HL, Ali S, Ross JS, Pavlick DC, **Bhanot G**, White EP, DiPaola RS, Lovell A, Cheng J, Ganesan S, Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer, J Clin. Invest. 2016;126(6):2334-2340. doi:10.1172/JCI84940. PubMed PMID: 27159395; PubMed Central PMCID: PMC4887167.
    b. Panda A, Betigeri A, Subramanian K, Ross JS, Pavlick DC, Ali S, Markowski P, Silk A, Kaufman H, Mehnert J, Sullivan R, Lovly CM, Sosman J, Johnson DB, **Bhanot G**, Ganesan S. Identifying a

clinically applicable mutation burden threshold as a biomarker of response to Immune Checkpoint Therapy in solid tumors, JCO Precision Oncology 2017: 1, 1-13. PubMed PMID: 29951597; PubMed Central PMCID: PMC6016848.

c. Panda A, Mehnert JM, Hirshfield KM, Riedlinger G, Demare S, Saunders T, Kane M, Sokol L, Stein MN, Elizabeth Poplin E, Rodriguez-Rodriguez L, Silk AW, Aisner J, Chan N, Malhotra J, Frankel M, Kaufman HL, Ali S, Ross JS, White EP, **Bhanot G**, Ganesan S, Immune Activation and Benefit From Avelumab in EBV-Positive Gastric Cancer, J Natl Cancer Inst. 2018, 1;110(3):316-320. doi: 10.1093/jnci/djx213 PubMed PMID: 29155997; PubMed Central PMCID: PMC6658862.

d. Panda A, de Cubas A, Stein S, Riedlinger G, Smith CC, Vincent BG, Beckermann KE, Ganesan S, **Bhanot G**, Rathmell WK, Endogenous retrovirus expression is associated with response to immune checkpoint inhibition in clear cell renal cell carcinoma, 2018, JCI-Insight. 2018 Aug 23;3(16); Smith CC, Beckermann KE, Bortone DS, de Cubas AA, Bixby LM, Lee SJ, Panda A, Ganesan S, **Bhanot G**, Wallen EM, Milowsky MI, Kim WY, Rathmell WK, Swanstrom R, Parker JS, Serody JS, Selitsky SR, Vincent BG. Endogenous retroviral signatures predict immunotherapy response in clear cell renal cell carcinoma. J Clin Invest. 2018 Aug 23. pii: 121476. doi: 10.1172/JCI121476. PubMed PMID: 30135306; PubMed Central PMCID: PMC6141170.

2. **Earlier work in Translational Medicine**: In previous work, we have developed novel methods to analyze microarray and RNA-seq data to show that ER+/HER2- tumors harboring amplification of Chr8q24.3, Chr8p11.2 or Chr17q21.33-q25.1 are likely to cause early recurrence and failure of hormonal therapy targeting the ER pathway5. In earlier work we also found that patients with HER2+ breast cancers with robust immune infiltration have better response to neo-adjuvant treatment with Herceptin.

   a. Bilal E, Vassallo K, Toppmeyer D, Barnard N, Rye IH, Almendro V, Russnes H, Børresen-Dale A-L, Levine a. AJ, **Bhanot G**, Ganesan S. (2012) Amplified Loci on Chromosomes 8 and 17 Predict Early Relapse in ER- Positive Breast Cancers. PLoS ONE 7(6): e38575. doi:10.1371/journal.pone.0038575. PubMed PMID: 27719901; PubMed Central PMCID: PMC3374812.

   b. Alexe G, Dalgin GS, Scanfeld D, Tamayo P, Mesirov J, Delisi C, Harris L, Bernard N, Martel M, Levine AJ, Ganesan S, **Bhanot G**. High Expression of Lymphocyte Associated Genes in node-negative HER2+ breast cancer correlates with lower recurrence rates. 2007, Cancer Research, 67, 10669:10676. PubMed PMID: 18006808; PubMed Central PMCID: PMC4887167.

3. **Viral Dynamics:** We have developed novel methods to study viral evolution to improve surveillance and vaccine strategies. In this context, we showed that the Influenza A H1N1 virus reduces its virulence over time by mimicking its hosts to avoid recognition by Toll-like receptors. In mammals, this is achieved by decreasing the number of dinucleotide CGs in its genomic sequence. We identified specific sequence motifs in the viral genome responsible for multi-organ immune response, likely to play a role in pandemics. Our findings provide a rationale for stratifying Influenza viruses by virulence potential. In a separate study, using protein sequences of Hemagglutinin from H5N1 strains from China, Egypt, and Southeast Asia in both avian and human hosts, we found that the human-derived strains arose from an identifiable subset of avian-derived strains, rather than from the complete avian pool. The human infecting avian strain subset have specific mutations in epitopic regions, receptor binding, glycosylation and polybasic cleavage sites of Hemagglutinin (HA). Further, we showed that targeted vaccines against these epitopes in avaians can create vaccines- escape-mutants unable to infect humans. Our results are important for H5N1 surveillance and control.

   a. Greenbaum BD, Levine AJ, **Bhanot G**, Rabadan R. Patterns of Evolution and Host Gene Mimicry in Influenza and Other RNA Viruses.2008, PLoS Pathogens 4(6):e1000079 PubMed PMID: 18535658; PubMed Central PMCID: PMC2390760.

   b. Wagh K, Bhatia A, Greenbaum BD, **Bhanot G**, Bird to Human Transmission Biases and Vaccine Escape Mutants in H5N1 Infections. PLoS One. 2014 2;9(7):e100754. PubMed PMID: 24988306; PubMed Central PMCID: PMC4079711.

4. Population Genetics: We have developed a number of techniques to analyze genome wide sequence data to identify phenotype associated polymorphisms and to infer migration patterns. Below are a few examples of such studies. (i) Protection against hyperlipidemia: In spite of a diet rich in lactose, fat and cholesterol, the Maasai in Kenya have low levels of blood cholesterol, and seldom suffer from gallstones or

cardiac diseases. Dietary studies suggested that they have a genetic adaptation for cholesterol homeostasis. By analyzing HapMap 3 data using a variety of metrics, we identified genomic regions and single nucleotide polymorphisms (SNPs) as strong candidates for recent selection in the Maasai for lactase persistence and cholesterol regulation. (ii) Novel phylogeny for human migration out of Africa: We developed a phylogeny inference method based on recursive Principal Component Analysis (PCA) which, applied to complete mtDNA sequences, revealed a novel phylogeny for human migrations out of Africa, which does not require back migration of the F clade. (iii) Longevity loci in the Japanese mtDNA: Using correlation and Principal Component analysis on complete mtDNA sequences, we found that polymorphisms associated with Haplogroup D4a are associated with extreme longevity in the Japanese population.

a. Wagh K, Bhatia A, Lukic S, Alexe G, Reddy A, Ravikumar V, Seiler M, Yao M, Boemo M, Cronk L, Naqvi A, Ganesan S, Levine AJ, **Bhanot G**. Lactase persistence and lipid pathway selection in the Maasai, PLoS ONE 2012, 7(9): e44751. PubMed PMID: 23028602; PubMed Central PMCID: PMC3461017.
b. Alexe G, Vijaya-Satya R, Seiler M, Platt D, Bhanot T, Hui S, Tanaka M, Levine AJ, **Bhanot G**. PCA and C lustering Reveal Alternate mtDNA Phylogeny of N and M Clades. 2008, J. Mol Evol, 67 (5), 465- 487. PubMed PMID: 18855041;
c. Bilal E, Rabadan R, Alexe G, Fuku N, Ueno H, Nishigaki Y, Fujita Y, Ito M, Arai Y, Hirose N, Ruckenstein A, **Bhanot G**, Tanaka M. Mitochondrial DNA Haplogroup D4a is a Marker for Extreme Longevity in Japan. 2008, PLoS ONE, 3(6): e2421doi:10.1371/journal.pone.0002421. PubMed PMCID: 18545700; PubMed Central PMCID: PMC2408726.
d. Alexe G, Fuku N, Bilal E, Ueno H, Nishigaki Y, Fujita Y, Ito M, Arai Y, Hirose N, **Bhanot G**, Tanaka M. Enrichment of Longevity Phenotype in mtDNA Haplogroups D4b2b, D4a and D5 in the Japanese Population. 2007, Human Genetics 121(3-4),347:356. PubMed PMID: 17308896.

5. Yeast Genetics and Ribosome Biology: Sporulation Efficiency Loci: Using Saccharomyces cerevisiae strains from the SGRP collection, we showed that 4 non-synonymous mutations in genes – HOS4, MCK1, SET3, and SPO74 are associated with sporulation efficiency across diverse yeast strains. Growth plasticity in yeast: Multi-QTL analysis identified loci previously known to be growth affecting QTL as well as novel two-QTL interactions affecting growth in Saccharomyces cerevisiae. A QTL that had no significant independent effect was found to alter growth rate and biomass for several carbon through two-QTL interactions. This suggests that adaptation is a multi-locus process. Antagonistic Pleiotropy (AP) in evolution. Comparing growth in favorable and stress conditions, a meta- analysis in yeast to identify the genetic basis of AP in bi-parental segregants, natural isolates, and a laboratory strain genome-wide deletion collection showed that there is abundant AP in synthetic crosses, but not in natural isolates. In deletion collections, organizational genes showed AP, suggesting ancient resolutions of trade- offs in basic cellular pathways. This suggests that multiple alleles maintain AP in natural populations to provide organisms with phenotypic flexibility. Intriguingly, we found that the RAS pathway is associated with maintenance of AP. Our results suggest that episodic fixation of AP in changing environments have created frozen-in instabilities in genetic networks which are often associated with diseases. The Modular Adaptive Ribosomes. Using large public datasets, we found that in yeast, the mRNA signature of the ribosome depends on environment, with several modules (groups) of ribosomal genes up/down regulated in a coordinated manner depending on environment. In complex eukaryotes such as humans and mice, the ribosome mRNA levels are tissue dependent, with blood, brain, testis tissue ribosomal expressions highly distinct from the rest. This suggests that the proteins used in the ribosome are not everywhere the same but are tissue dependent. Most recently (manuscript in preparation), we have shown that ribosome mRNA levels in tumors are also tissue specific and, in some cases, have multiple subtypes in a given tissue with distinct recurrence and overall survival.

a. Tomar P, Bhatia A, Ramdas S, Diao L, **Bhanot G**, Sinha H. (2013) Sporulation Genes Associated with Sporulation Efficiency in Natural Isolates of Yeast. PLoS ONE 8(7): e69765. Do i:10.1371/journal.pone.0069765. PubMed PMID:23874994; PubMed Central PMCID: PMC3714247.
b. Bhatia A, Yadav A, Zhu C, Gagneur J, Radhakrishnan A, Steinmetz LM, **Bhanot G**, Sinha H. Yeast growth plasticity is regulated by environment-specific multi-QTL interactions. Genes, Genomes, Genetics (G3), 2014 Jan 28;4(5):769-77. Doi:10.1534/g3.113.009142. PubMed PMID:24474169; PubMed Central PMCID: PMC4025475.

c. Yadav A, Radhakrishnan A, **Bhanot G** and Sinha H. Regulation of Antagonistic Pleiotropy in Natural and Recombinant Yeast Populations Suggests its Role in Adaptation. G3: Genes, Genomes, Genetics, May 1, 2015 vol. 5 no. 5 699-709. doi: 10.1534/g3.115.017020. PubMed PMID: 25711830; PubMed Central PMCID: PMC4426359.
d. Yadav A, Radhakrishnan A, Panda A, Singh A, Sinha H, **Bhanot G** (2016) The Modular Adaptive Ribosome. PLoS ONE 11(11): e0166021. doi:10.1371/journal.pone.0166021. PubMed PMID: 27812193; PubMed Central PMCID: PMC5094737.