Bioinformatics: genomics to phenomics and beyond

The commentary 'Bioinformatics: how it helps to boost modern biological research'[1] aptly summarizes how modern bioinformatics has moved from simple mapping and sequencing to the era of functional genomics. We would like to supplement new and exciting developments which may result in an overall paradigm shift in bioinformatics and related *in silico* data domains. First, it is to be appreciated that plant phenotyping, a relatively novel field, involves high-throughput plant phenomic platforms that accurately measure trait values and variability across crop genotypes[2]. A dialogue of phenomics with genomics (and vice versa) seems to be operative ushering in a big-data era that shall see a synthesis of traditional omics (genomics, transcriptomics, metabolomics) and phenomics as never before[2,3]. Secondly, there is the emerging field of phenotype prediction where the physico-chemical characteristics of an organism are predicted from knowledge of its genotype and environment. Such studies, often called genome-wide association studies, are of central importance to a variety of applied areas, including medicine and crop-breeding. For example, Greinberg *et al.*[4] reported a machine learning-based phenotype prediction on simple yeast, and complex rice and wheat systems. Thirdly, the traditional ecological and evolutionary problems are being addressed using modern molecular approaches to identify genomic mechanisms governing ecologically important traits as mediated through pathways controlling morphology, physiology, development and behaviour[5]. These and other developments shall need parallel storage, retrieval and processing of a mind-boggling quantum of biological mega-data sets in the following decades.

1. Barik, S., Rai, N., Mishra, P., Singh, S. K. and Gautam, V., *Curr. Sci*., 2020, **118**, 589–599.
2. Pratap, A. *et al*., *Agronomy*, 2019, **10**, 126.
3. Zhao, G. Y. J., Guo, X., Wen, W., Gu, S., Wang, J. and Fan, J., *Front. Plant. Sci*., 2019, **10**, 714.
4. Grinberg, N. F., Orhobor, O. I. and King, R. D., *Mach. Learn*., 2020, **109**, 251–277.
5. Morgan, T. J., Herman, M. A., Johnson, L. C., Olson, B. J. C. S. and Ungerer, M. C., *Genome*, 2018, **6**, 5–7.

RAJIV ANGRISH[1,*]
SARITA DEVI[2]

[1]*#741, Sector 4, Panchkula 134 112, India*
[2]*Department of Botany and Plant Physiology, CCS Haryana Agricultural University, Hisar 125 004, India*
**e-mail: angrish2004@gmail.com*

Deciphering asymptomatic malaria – the missing link in India's fight against the disease?

According to the World Malaria Report 2019, there has been a reduction in malaria cases worldwide by approximately 23 million during 2010–18 (ref. 1). However, data does not suggest a significant case reduction from 2017 to 2018 globally. India, interestingly, showed a reduction of 2.6 million malaria cases in 2018 compared to 2017 (ref. 1). This is encouraging since most other high-burden African countries reported an increase in disease burden. As India moves towards its goal of malaria elimination by 2030, the focus has shifted to controlling hidden and underexplored niches of infection such as asymptomatic and sub-microscopic malaria. Studies conducted across different epidemiological settings in India over the past few years roughly peg the asymptomatic malaria burden anywhere between 18% and 71% (ref. 2). Identification of these cases, accurate diagnosis and evaluation of their actual role in persistence and transmission of the malaria parasite present unique challenges. As we delve deeper into the mechanics of appropriate elimination strategies to be adopted given the time and monetary constraints, a better understanding of the role that these asymptomatic cases might play in elimination strategies is warranted.

The general consensus is that asymptomatic malaria cases act as reservoirs of infection in the community. Usually associated with low parasite densities, these cases escape detection by conventional tests such as microscopy and rapid diagnostic kits which are routinely used for surveillance in resource-limited settings, e.g. remote villages, forest fringe and hilly areas in India, where most of the transmission is confined. Asymptomatic and sub-microscopic cases harbour gametocytes which can be transmitted to vectors under suitable conditions, thus maintaining a steady circulation of parasites in the community[3]. Gametocyte density and duration of infection are the two characteristics that determine the transmission potential[4]. However, the gametocyte carriage rate and density vary considerably in high transmission versus low transmission settings. Also, there is no clear association between asexual parasite density and gametocyte density; both positive and negative correlations have been observed[5]. Gametocytes have been shown to persist in peripheral blood for several weeks following clearance of asexual parasitaemia; persistence up to 55 days after non-ACT (Artemisinin Combination Therapy) based treatments and up to 13.4 days following ACT-based treatments has been observed[6]. However, what proportion of these gametocytes is actually infective to the *Anopheles* vector is still inconclusive. Results from field studies have so far not been able to provide a clear picture of the host and parasite characteristics, gametocyte density, vector dynamics, transmission settings and environmental conditions that might affect the actual transmission of infection from these asymptomatic hosts to the mosquito vectors and subsequently to uninfected individuals[7]. A study from Colombia

reported that almost 57% of asymptomatic malaria cases were infective to mosquito vectors, which was similar to that observed in acute cases. However, the intensity of infection as demonstrated by oocyst density was significantly lower in the asymptomatic cases[8]. On the other hand, researchers from Brazil found an infection rate of only 1.42% in asymptomatic malaria cases caused by *Plasmodium vivax*[9]. Whether the same is applicable in India is debatable since both *Plasmodium falciparum* and *P. vivax* are the major parasite species prevalent here and the vectors are also different. Reports from other countries in Southeast Asia have shown a positive correlation between the number of gametocytes and infection rate in *Anopheles dirus*[9]. Results from other malaria endemic areas of the world are more scattered[9]. In addition, there are other determinants such as host immunity, vector characteristics, ecological and seasonal variations that might play a role in the transmission of gametocytes from asymptomatic and sub-microscopic cases to *Anopheles* vectors[7]. These need to be evaluated using comprehensive field and laboratory studies. Elimination strategies should be directed by such evidence-based research since the malaria parasite is highly evolved and the disease itself has dozens of determinants unique to each epidemiological setting.

In the Indian context, asymptomatic malaria thus remains a challenge, with problems in case detection, treatment, follow-up, recrudescence and reinfection. Newer and improved point-of-care molecular diagnostics have to be developed for field use, and additional interventions to target the parasite reservoir like mass drug administration (MDA) and mass screen and treat (MSaT) strategies might find application in the near future in select areas[10]. Till then, existing tools and vector control measures have to be used in combination under appropriate settings to keep the situation under control. Newer and robust surveillance techniques and geo-linked epidemiological data are likely to play an important role towards possible elimination of malaria in the near future.

Conflict of interest: The authors declare no competing financial or non-financial interests.

1. WHO, World Malaria Report 2019. World Health Organization, Geneva, Switzerland, 2019.
2. Van Eijk, A. M. *et al*., *Sci. Rep*., 2019, **9**(1), 17095.
3. Ouedraogo, A. L. *et al*., *J. Infect. Dis*., 2016, **213**(1), 90–99.
4. Lin, J. T., Saunders, D. L. and Meshnick, S. R., *Trends Parasitol*., 2014, **30**(4), 183–190.
5. Ouedraogo, A. L. *et al*., *Malar. J*., 2010, **9**, 281.
6. Bousema, T. *et al*., *Malar. J*., 2010, **9**, 136.
7. Meibalan, E. and Marti, M., *Cold Spring Harb. Perspect. Med*., 2017, **7**(3).
8. Vallejo, A. F., Garcia, J., Amado-Garavito, A. B., Arevalo-Herrera, M. and Herrera, S., *Malar. J*., 2016, **15**, 48.
9. Martins-Campos, K. M. *et al*., *Parasit. Vectors*, 2018, **11**(1), 288.
10. Lindblade, K. A., Steinhardt, L., Samuels, A., Kachur, S. P. and Slutsker, L., *Expert Rev. Anti-infect. Ther.*, 2013, **11**(6), 623–639.

SAURAV JYOTI PATGIRI[1,*]
DIBYA RANJAN BHATTACHARYYA[1]
IPSITA PAL BHOWMICK[1]
MD ATIQUE AHMED[2]

[1]*Malaria Division,*
ICMR-RMRC Northeast Region,
Dibrugarh 786 001, India
[2]*DBT-Ramalingaswami Re-entry Fellowship,*
ICMR-RMRC Northeast Region,
Dibrugarh 786 001, India
**e-mail: saurav.patgiri@gmail.com*