In search of target in *Plasmodium falciparum* using *in silico* methods.

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The process of drug discovery is considered as one of the longest and costliest efforts. The classical approach to drug discovery process is the identification of drug target, then designing the lead compound, and finally to the validation of the compounds through clinical trials. It was considered that on an average one new drug takes approximately 12–13 years to reach to a patient from a research lab. Millions have been spent to find some new drug candidates for the particular disease, but the success rate is very low: the reason is the limited knowledge of complex biological systems. Therefore, it was perceived that until in-depth knowledge of complex biological process that leads to the diseased state is considered, the discovery of new drug will be a time-consuming and challenging process.

Drug target identification is considered as one of the most crucial and strenuous processes in drug designing. Effective drug target identification not only assists in improving the efficacy of the drug but also helps in avoiding the potential side effects; many failures could be avoided in early phase. In order for the drug target to be effective, it must be essential for its growth, replication, and survival of the microorganism. According to the pharmacological definition, drug targets can either be inhibited or activated by the drug molecule by the binding of the drug molecule. The sequencing of various genomes including those organisms which are involved in various infectious diseases has paved the way to identify novel drug targets from the analysis of gene networks.

In case of signal transduction related drug targets, network-based drug target identification approach has been in spotlight in recent years. With the availability of advance methods of data generation, it is comparatively apparent to validate the model generated for a process with the experimental results. Thus, the interconnectivity between different levels of understanding becomes critical to analyze the data and build the novel predictions. Such effort has developed many websites and links for novel targets to attack malaria and related parasite disease(http://plasmodb.org/plasmo/, http://www.atgc-montpellier.fr/PlasmoDraft/) . One example of a platform which has integrated well known gene product/targets & chemicals to inhibit is Pfaldb (http://pfaldb.jnu.ac.in/Malaria/homeHit.action).

But it is observed that the relationship between the data generated from various platforms is nonlinear and dynamic which makes the process of model building a highly challenging effort. More or less no correlation between the protein expressed and kinetics of the enzymes in cellular system as compared to the single enzyme assay in test tube makes the prediction of target using simple comparative genomics and proteomics rather futile. To resolve such relevant challenges there have been many attempts, experimentally and *in silico*. Amongst so far known methods, kinetic modeling offers a great way to capture the dynamics of a biochemical reaction network in mathematical form so as to analyze and simulate its behaviors and ultimately to use the model to answer real physiological questions.

The methylerythritol phosphate (MEP) pathway of *Plasmodium falciparum* (*P. falciparum*) has become an attractive target for anti-malarial drug discovery. This study describes a kinetic model of this pathway, its use in validating 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR) as drug target from the systemic perspective, and additional target identification, using metabolic control analysis and in silico inhibition studies. In addition to DXR, 1-deoxy-D-xylulose 5-phosphate synthase (DXS) can be targeted because it is the first enzyme of the pathway and has the highest flux control coefficient followed by that of DXR. *In silico* inhibition of both enzymes caused large decrement in the pathway flux. This study demonstrates that both types of enzyme targets, one acting via flux reduction and the other by metabolite accumulation; exist in P. falciparum MEP pathway. These groups of targets can be exploited for independent anti-malarial drugs.

References:

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