Fighting malaria through metabolism

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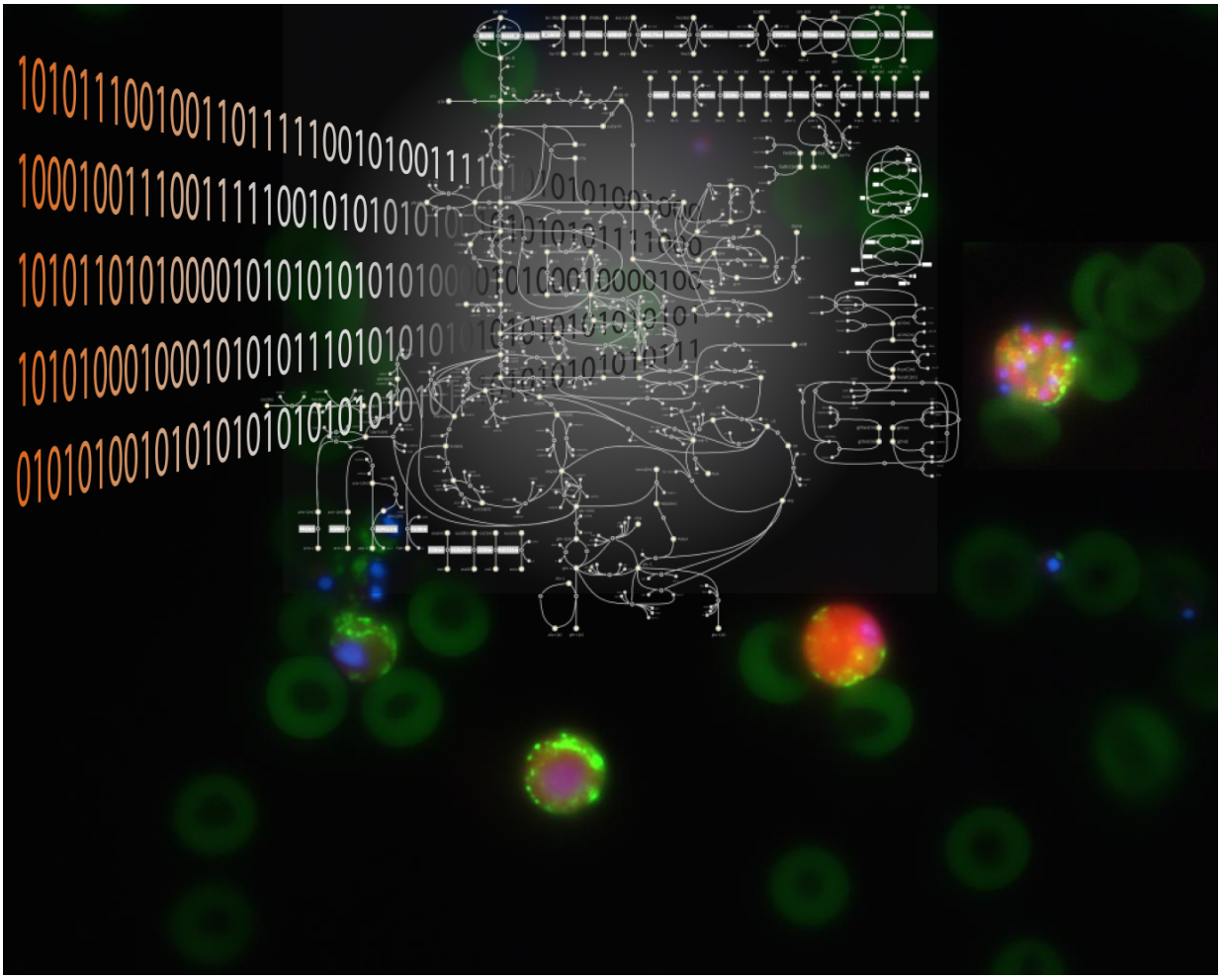

Computational analysis of the malaria parasites' metabolism aids in the understanding of observed phenotypes. Red fluorescent *Plasmodium berghei* parasites infect green fluorescent mouse erythrocytes. Credit: V. Heussler (University of Bern; fluorescent malaria parasites)/ K.C. Soh M, L. Miskovic (EPFL; metabolic network)/ V. Hatzimanikatis, A. Chiappino-Pepe (EPFL; composite image)

EPFL scientists have fully modeled the metabolism of the deadliest malaria parasite. The model offers unprecedented tools for developing a new generation of antimalarial therapies to overcome drug resistance.

Many of the malaria parasites develop resistance to drugs. A promising strategy is to target the parasite's metabolism, but it has proven very complicated to connect to their genetics. EPFL scientists have now developed the first ever mathematical model of a malaria parasite that accurately integrates its genetics and metabolism, opening a whole new way of treating the disease. The model is based on the deadliest of the malaria parasites, *Plasmodium falciparum*, and is published in *PLoS Computational Biology*.

There have been intensive research efforts to map out and target metabolic enzymes of the *Plasmodium* parasites. But their metabolism has proven to be versatile and complex, and integrating all existing data on the parasites' genetics to their metabolism is challenging.

A new model of malaria parasites' metabolism

The lab of Vassily Hatzimanikatis at EPFL, with colleagues at Geneva and Bern, has now developed a new mathematical model of the malaria parasite *P. falciparum*. The model connects the experimental data from both genetics and metabolomics, which is the study of all the metabolic processes of an organism and maps out all of its metabolites.

Malaria parasites infect various cells through their life cycle, displaying different points of vulnerability at each life stage. However, there has not been a comprehensive attempt to investigate the enzymes that are consistently vulnerable.

The scientists studied *P. falciparum* but instead looked at the way the parasites produce and use energy for their metabolic reactions. This approach can help identify which metabolic functions are essential at each stage of the infection, and which are energetically coupled through key metabolites.

The scientists could therefore model, for the first time, the bioenergetics of the metabolism of *P. falciparum*, predicting with unprecedented accuracy which genes are indispensable for every biological function in the parasite.

By integrating metabolomics and genetics data, the model reveals the complex interactions between gene products, reactions, and metabolites in the parasite, and identifies potential mechanisms to target with drugs.

"The design of efficient antimalarial drugs that target the parasites and not the patient's metabolism requires an in-depth understanding of the mechanisms that make a particular enzyme essential," says Anush Chiappino-Pepe, the Ph.D. student who carried out the study at Hatzimanikatis' lab. "So mathematical modeling of the parasite's metabolism becomes a very powerful tool."

The EPFL scientists will continue to improve the model with genetics and metabolomics data generated by the MalarX.ch consortium, which involves the University Geneva and Bern, and the Wellcome Trust Sanger Institute. They aim to reveal the mechanisms behind host-pathogen interactions and gain insight into the physiology of the parasite while it is dormant.

This work included a contribution from the University of Geneva (Faculty of Medicine).

More information: Anush Chiappino-Pepe, Stepan Tymoshenko,

Meriç Ataman, Dominique Soldati-Favre, Vassily Hatzimanikatis. Bioenergetics-based Modeling of Plasmodium falciparum Metabolism Reveals its Essential Genes, Nutritional Requirements, and Thermodynamic Bottlenecks. *PLoS Computational Biology* 23 March 2017. DOI: 10.1371/journal.pcbi.1005397