

Intra- and Inter- cellular network analyses for characterizing pathogen-host interactions

Arvind K. Chavali, Brian J. Schmidt, Jeffrey D. Whittemore, James A. Eddy, Kyle T. Williams, Michael B. Lawrence and Jason A. Papin*

Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, USA

*E-mail: papin@virginia.edu

For intracellular networks, the stoichiometric matrix reconstruction and associated systems analysis techniques have facilitated the interrogation of biological systems on the genome-scale (Becker & Palsson, 2005; Forster et al, 2003; Schilling et al, 2002). Models of biochemical networks with predictive capabilities can be constructed by assimilating available genomic, proteomic, and metabolomic data (Forst, 2006). For example, a metabolic network reconstruction uses a compilation of data from public databases and published literature to generate gene-protein-reaction (GPR) relationships (Reed et al, 2006). Subsequently, systematic genetic knockouts of reactions in the resultant cellular network and assessment of robustness of particular enzyme-catalyzed reactions at a scale of hundreds of reactions enables evaluation of the efficacy of potential drug targets (Becker & Palsson, 2005).

For multi-cellular processes, agent-based modeling utilizes a bottom-up systems biology approach to simulate complex, uncertain, non-linear and dynamical biological systems composed of “agents” interacting spatially and temporally in a defined “world” space (Grimm et al, 2005). Perturbations on the rules governing interactions can give much insight into the system and yield a new set of hypotheses that can be experimentally validated.

Here we present the intracellular metabolic network reconstruction of *Leishmania major*. The network was comprised of 510 genes and 1007 metabolites (Table 1). Approximately 66% of all reactions were gene-associated, with the non-gene associated reactions mainly comprising transport reactions (between sub-cellular compartments and between the cytosol and extra-cellular space). *L. major* metabolism was found to be highly compartmentalized, with 881 reactions spanning 8 different sub-cellular localizations.

In addition, we also present an agent-based model of CD4⁺ T-cell and dendritic cell interactions within paracortical area (or T-cell zone) of a lymph node infected by *L. major*. Different strains of mice have varied responses to *L. major* infection: C57BL/6J mice are resistant, while BALB/c mice are susceptible. Effector T-helper cell polarization has been attributed to the differential outcomes in the two strains with a T-helper 1 (T_{H1}) response leading to resistance and T-helper 2 (T_{H2}) causing susceptibility (Santos et al, 2006; Baldwin et al, 2004). The agent-based model focused on factors involved in T-cell polarization including T-cell receptor (TCR) and major histocompatibility complex (MHC)-associated peptide affinity, co-stimulatory molecule effects and cytokine signals (Kapsenberg, 2003). Each of these factors was varied to determine respective influence on the final T-cell decision. Simulations were run for 12-week time-points and proportions of T_{H1}, T_{H2}, T-regulatory (T_{REG}) and T-non polarized (T_{NP}) cells were documented. Hence, a relationship was formed between weights of factors involved in T-cell polarization and final disease outcome.

Genes	510
Reactions	881
Gene-Associated Rxns	582
Non-Gene Associated Rxns	299
Metabolites	1007
Compartments	8

Table 1: *L. major* metabolic network characteristics

Ultimately, the intracellular metabolic network and multi-cellular agent-based model will be coupled in the future to shed considerable light on *L.major*'s pathogenesis. This will give rise to a rigorous multi-scale systems level understanding of pathogen-host interactions.

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