

Modular design of multiscale models, with an application to the innate immune response to fungal respiratory pathogens

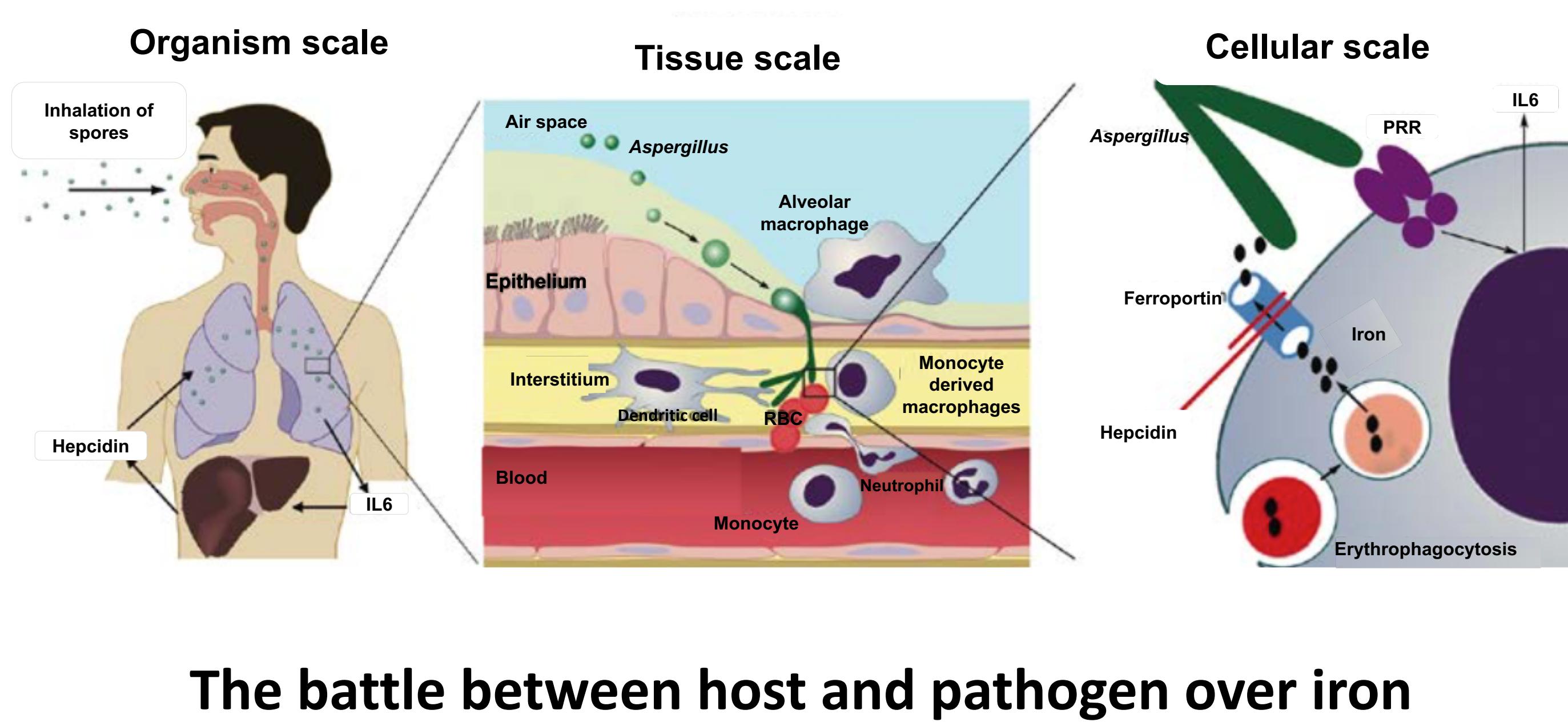
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Project Goals

- Novel modular design principles for multiscale models that enhance their extensibility, usability, interoperability, and reproducibility.
- A multiscale model of the innate immune response to fungal pulmonary pathogens that focuses on the "battle over iron" between host and pathogen, with the goal of developing host-centric therapeutic approaches.
- An interactive visual model interface that enables the use of the model without requiring modeling expertise.
- An information management platform for the wide range of heterogeneous data associated with the project, with the aim of making the model credible and reproducible.

Invasive Aspergillosis



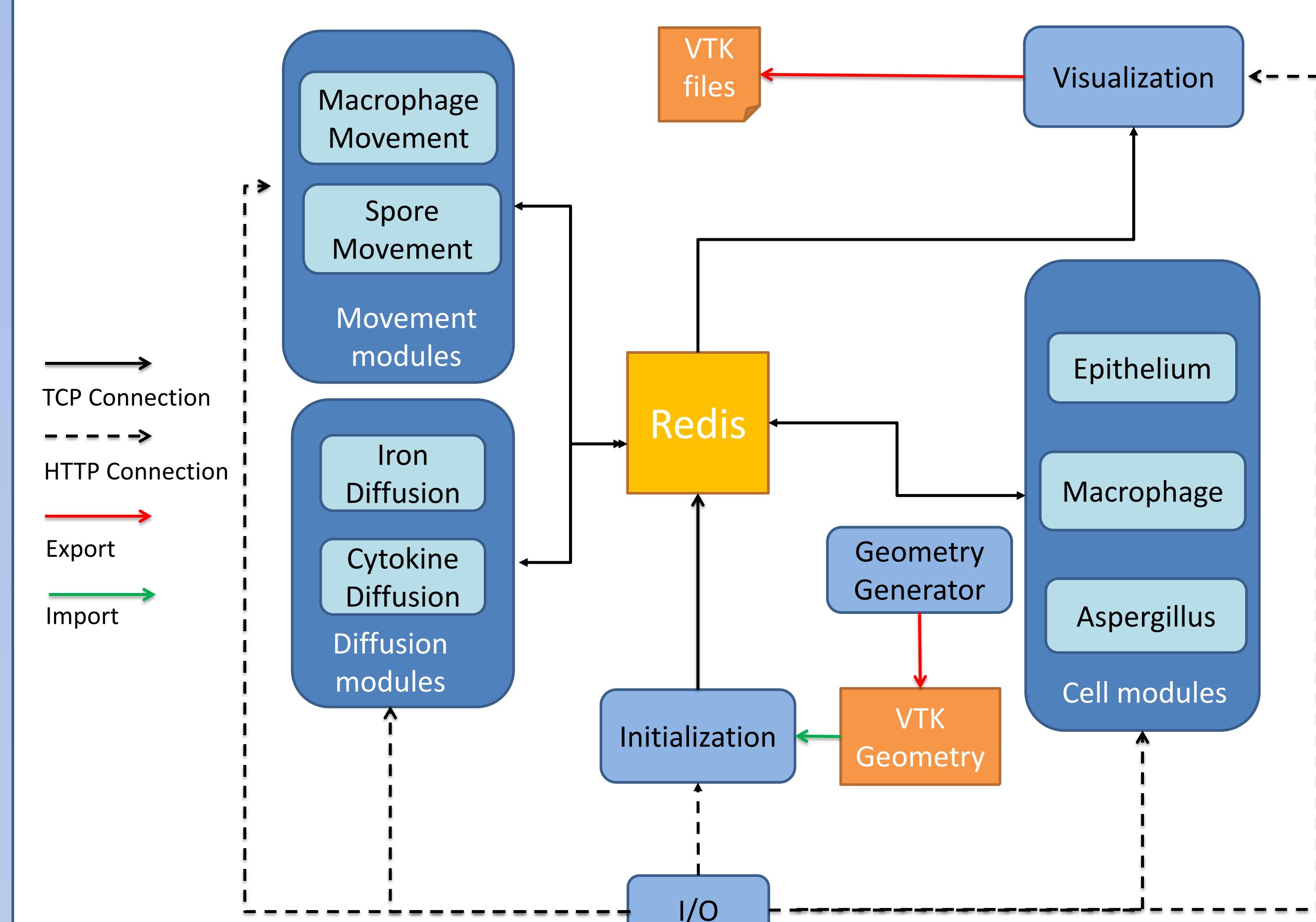
Mathematics at different scales

Intracellular scale: Generalized Boolean networks in fungal cells, macrophages, dendritic cells, and neutrophils capture a molecular network that combines effects of the immune response with iron homeostasis pathways.

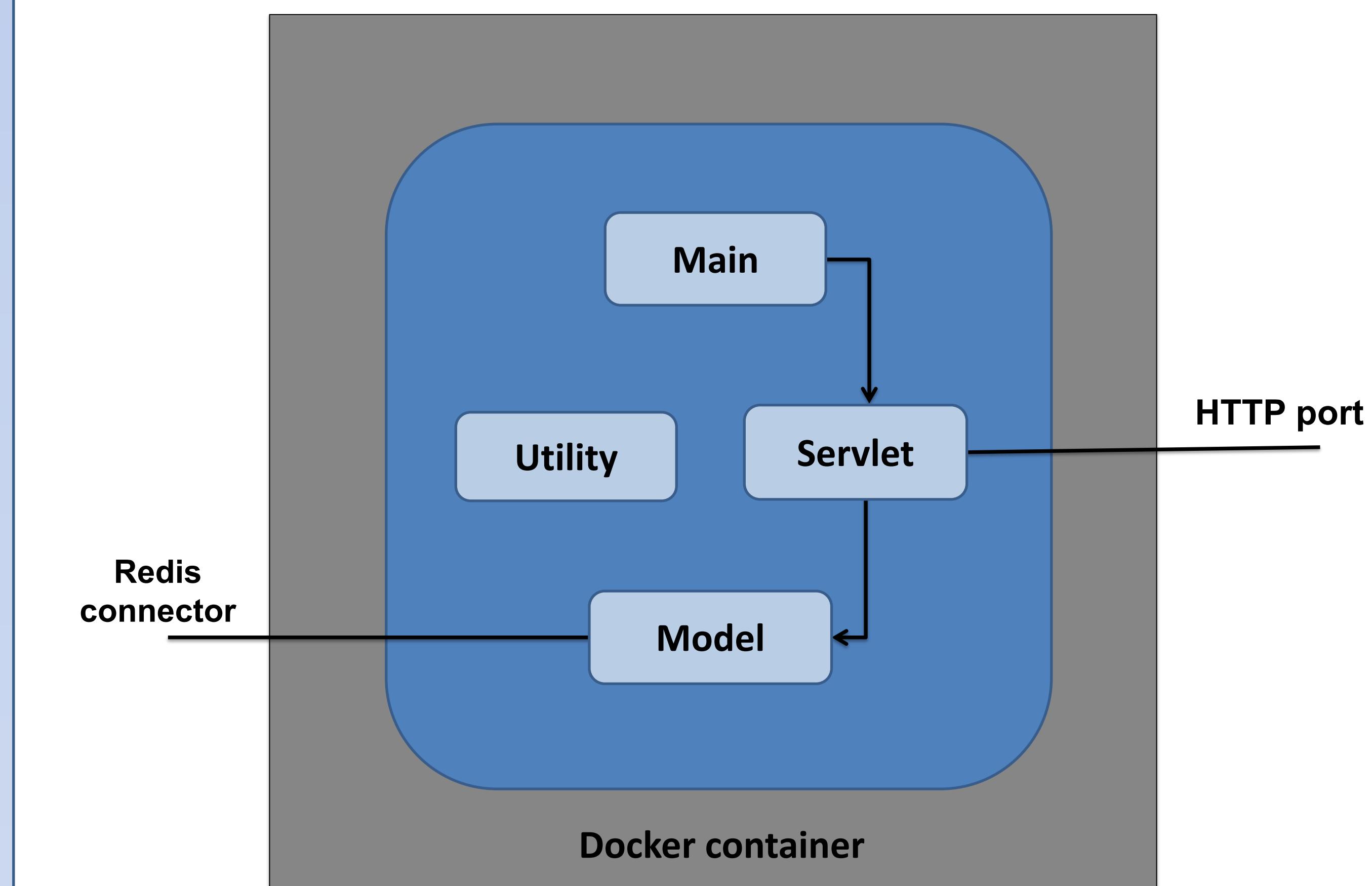
Tissue scale: An agent-based model captures the movement and interactions of cells, as well as the diffusion of molecules, in an alveolar structure representative of the end of the respiratory tree. Diffusion of molecules, such as iron, IL-6, and hepcidin, is implemented through partial differential equations.

Whole-body scale: An equation-based input-output model captures the relationship between IL-6, secreted by cells at the tissue scale and transported to the liver, and the hormone hepcidin, synthesized by the liver and transported to the lung tissue. Transport by the circulatory system is represented by equations calibrated with in vivo measurements.

Software Architecture

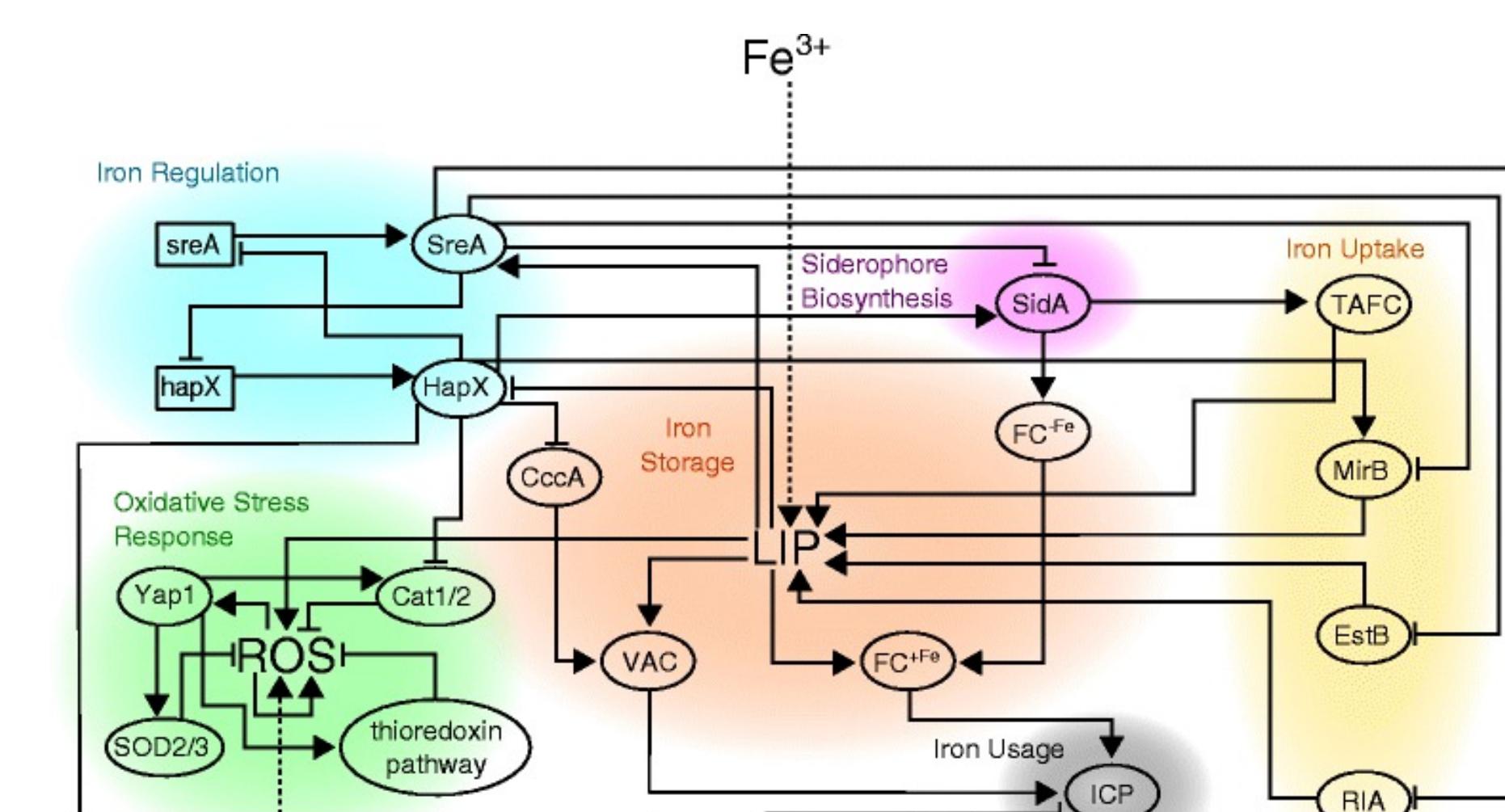


Module Structure

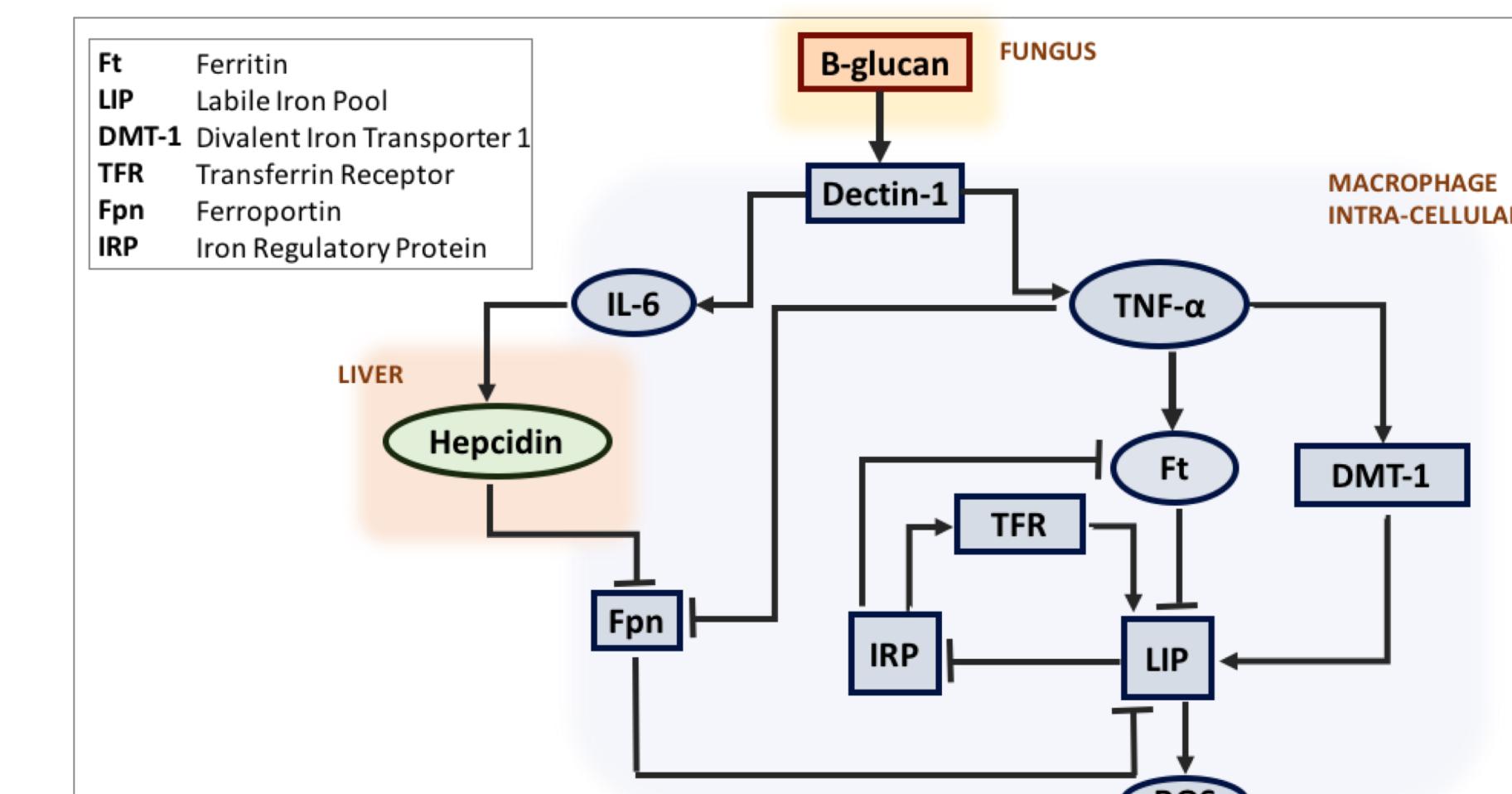


Intracellular models

A. fumigatus

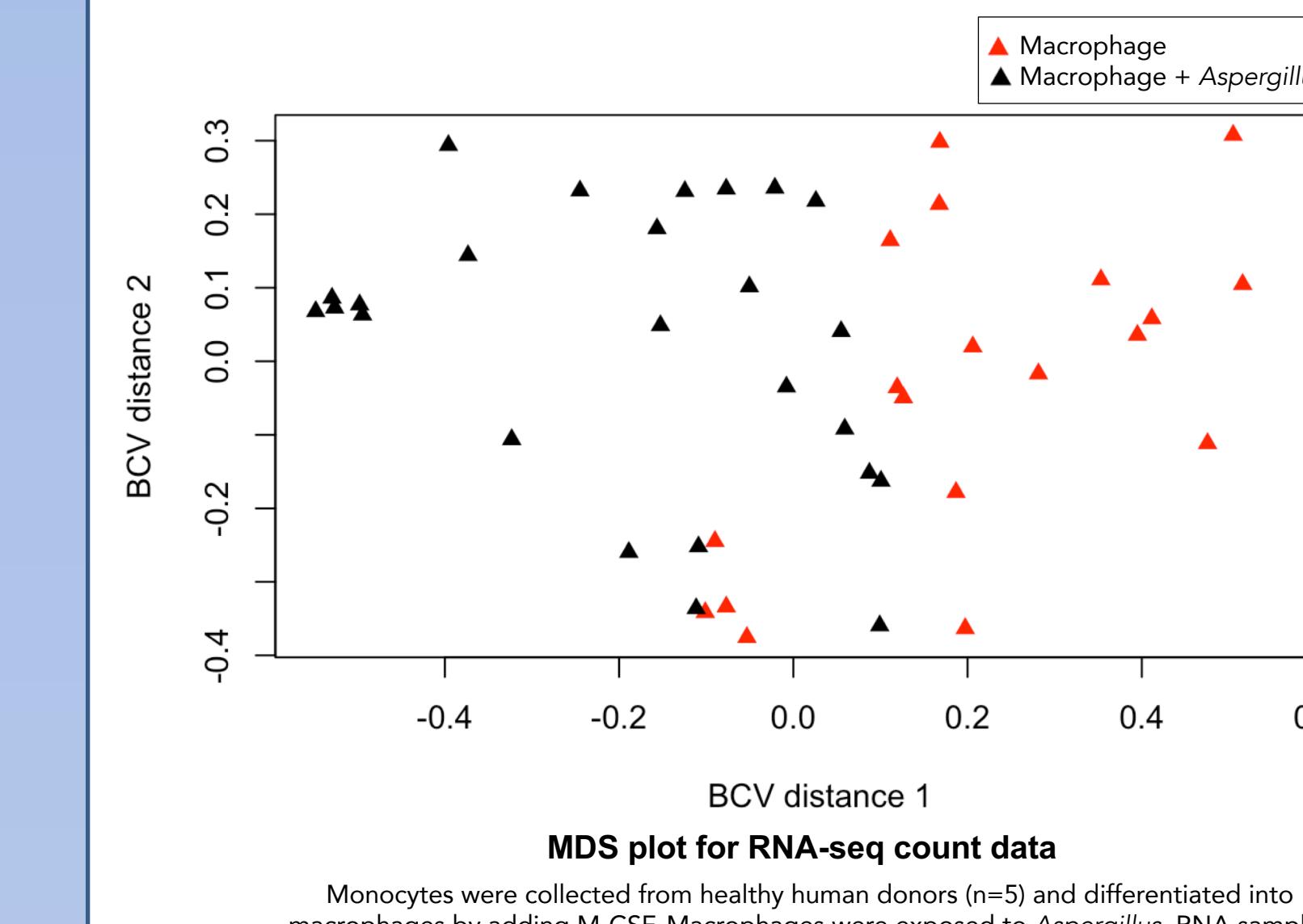


Macrophage (Preliminary)

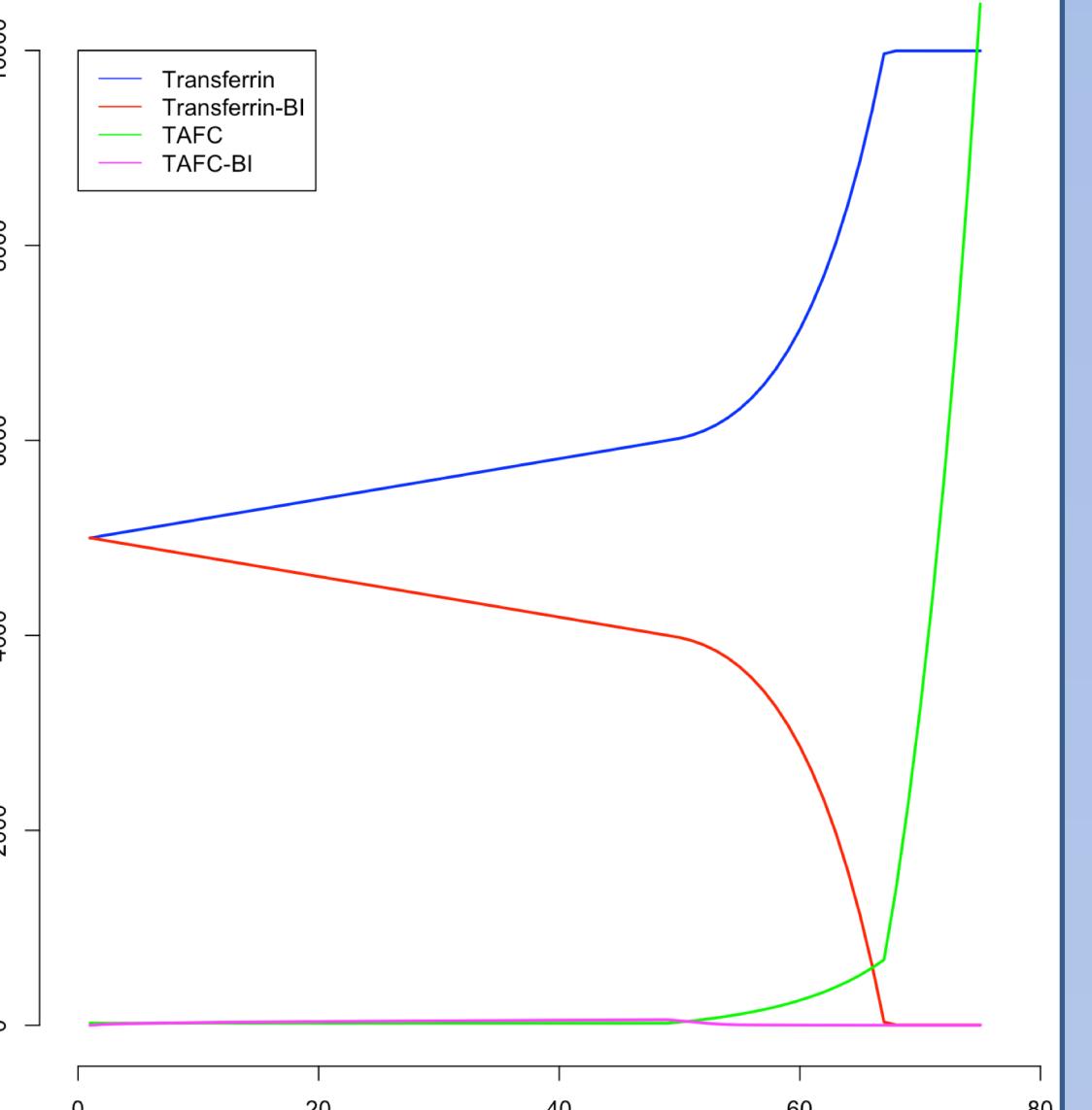


Data

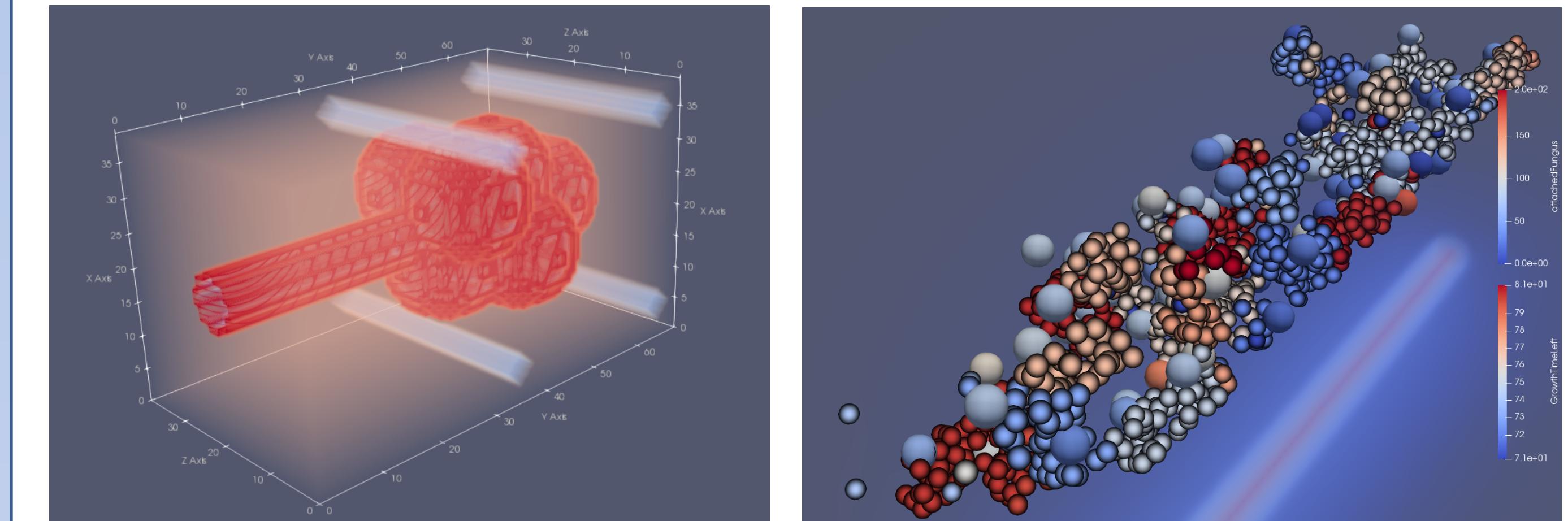
Experimental Data



Simulation Data



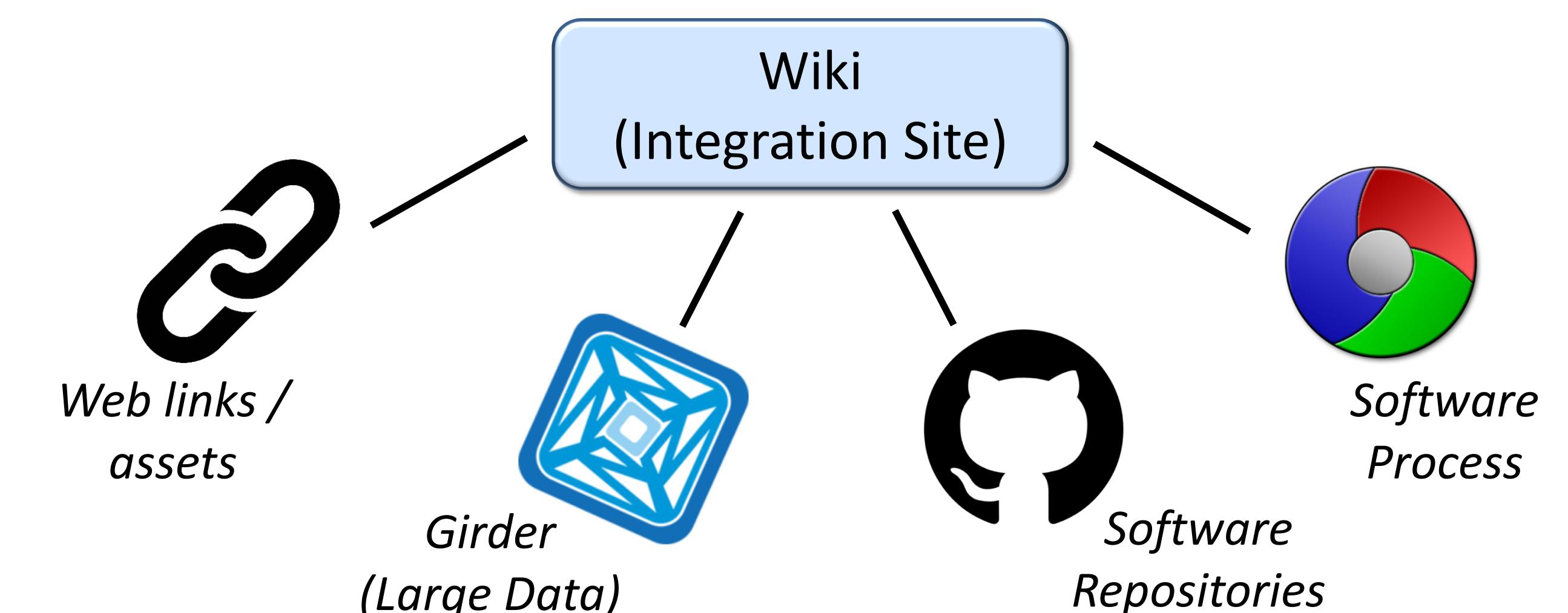
Modeling & Visualization



Simulation model consists of volumetric voxel grid for diffusion equations and implicit geometric/tissue definition, with point sprites representing spores and immune cells.

Integrated, web-based visualization uses the open source systems VTK / VTK.js, directly interfacing with simulation data hosted by the information management system. Multiscale probing, viewing, and temporal animation is provided.

Information Management



Heterogeneous data. Support complex, mixed, and large data and metadata through a linked collection of data management resources. This includes experimental lab notebooks, software repositories, RNA-seq, simulation results, Docker modules, and publications / documentation.

Web- and cloud-based. Data resources are cloud-based and available through web interfaces thereby maximizing accessibility, ease of use, and data backup. Cloud-systems (based on open source Girder) enable scalability and support remote execution to minimize large data transport.

Credible and reproducible. Open science practices ensure credible and reproducible approaches. Over the course of the project publications, data, and methods will be published and available to the scientific community.