Status report: parameter estimation of a large-scale mechanistic model for mast cells in asthma

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Background: Asthma is a complex disease involving various heterogeneous mechanisms. A deeper understanding of the heterogeneity of asthma is needed for better diagnosis and therapy. To this end, the development of a mechanistic description of asthma mechanisms was initiated, the AsthmaMap (http://disease-maps.org/projects/asthma).

Objective: Our work employs the AsthmaMap to build a mechanistic model of mast cell dynamics, improving our understanding of the disease and offering a tool for predicting the efficacy of medications. Here we aim to develop a predictive model which integrates qualitative knowledge about the pathway topology and quantitative experimental data available in the literature.

Methods: We employed the expertise of several domain experts to derive a Systems Biology Markup Language (SBML) model from the mast cell part of the AsthmaMap and additional literature. For the simulation and parameterizations of the SBML model, we used the MATLAB toolboxes AMICI (Fröhlich et al., 2017, PMID 28114351) and PESTO (Stapor et al., 2018, PMID 29069312). Quantitative experimental data were extracted from several published studies (e.g., Parravicini et al., 2002, PMID 12089510).

Results: We obtained an SBML model with CellDesigner markup for mast cell signalling, which has more than 300 species and 400 parameters, and includes kinetic laws for all reactions. Additionally, we established a pipeline for building a data repository, which is used for the model parameterization. Preliminary results indicate that the parameterization of the model is challenging, due to nonlinear dynamics. However, the current model already captures several aspects of the mast cell response to allergens.

Conclusion: Our study has shown that the translation of a disease map to a mechanistic computational model is a complex process involving a series of steps, among others the establishment of a repository of quantitative experimental data. In the future, this repository might be built alongside the disease map. Overall, we have made substantial progress towards the development of a predictive model for mast cell dynamics.