

Analysis of clinical pathology parameters and histopathologic findings from eTOX

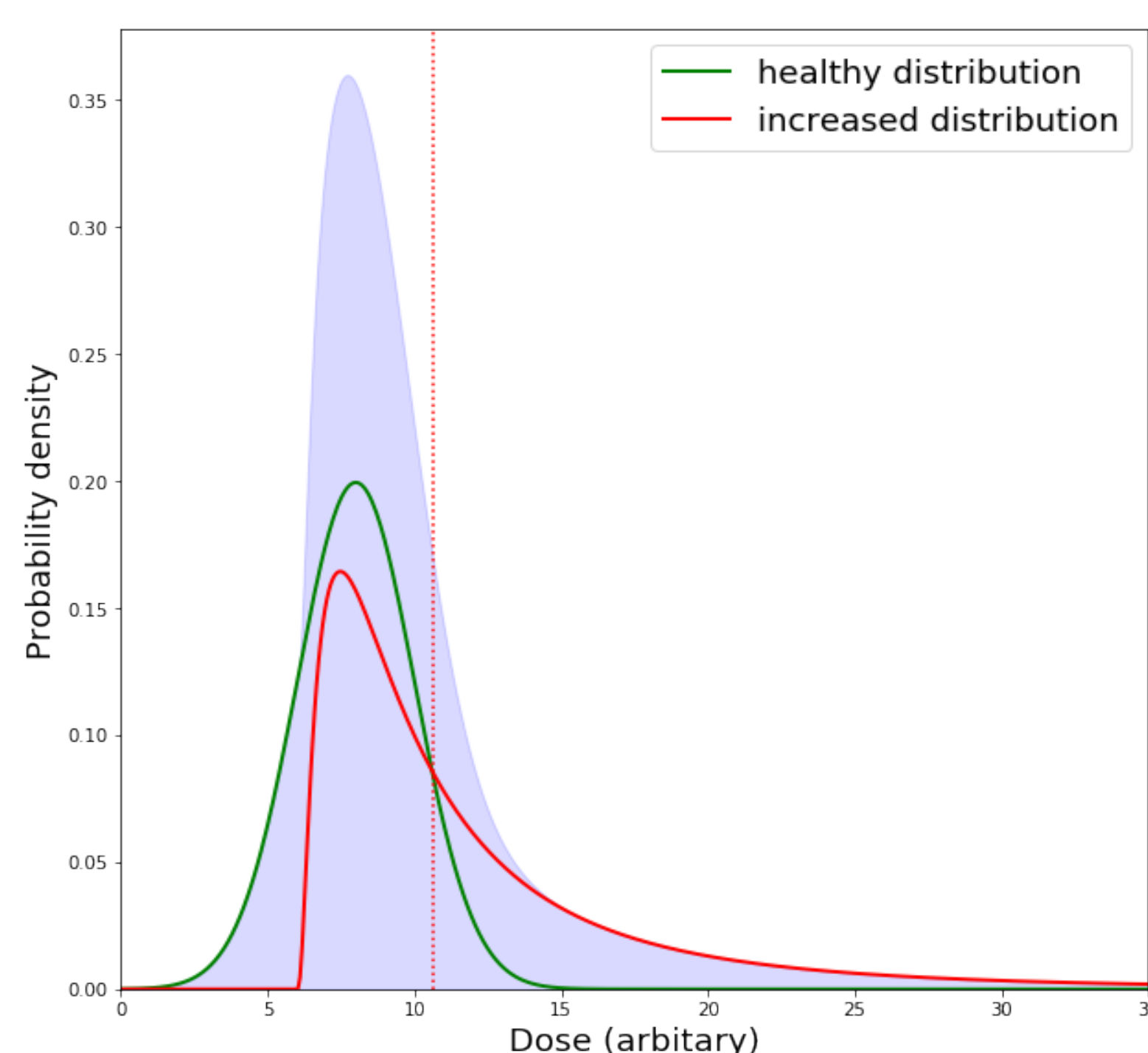
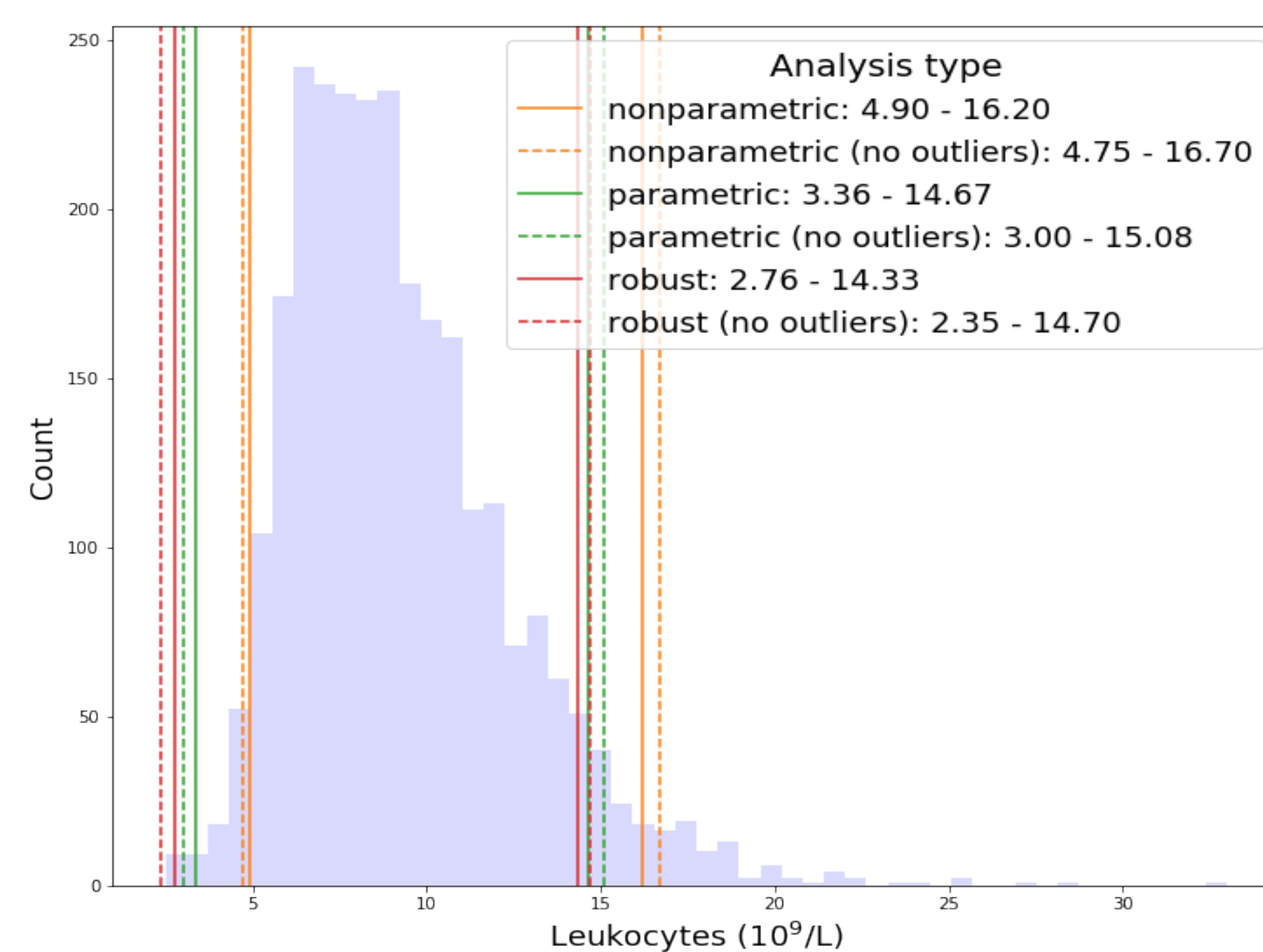


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Overview

Preclinical toxicology data from the eTOX project (Sanz *et al.*, *Nature Reviews Drug Discovery*, 16 (2017), 811–812) was analysed to provide background rates and treatment-related values on clinical pathology and histopathology datasets. Reference intervals and distributions for 20 of the most common clinical pathology parameters in rat and dog were generated, decision thresholds were applied to relabel data considered to be anomalous, and maximum fold change estimates calculated for each of these parameters. Background histopathology incidence rates in the liver, heart and kidney were also generated, with anomalous data relabelled using a Bayesian model to identify dose-dependent increases in pathologies. The outputs from this study include a mechanism for analysing newly generated data, rates and distributions that can be used to build predictive dose-response models, and a means to correlate treatment-related clinical pathology findings with concurrent histopathology findings.



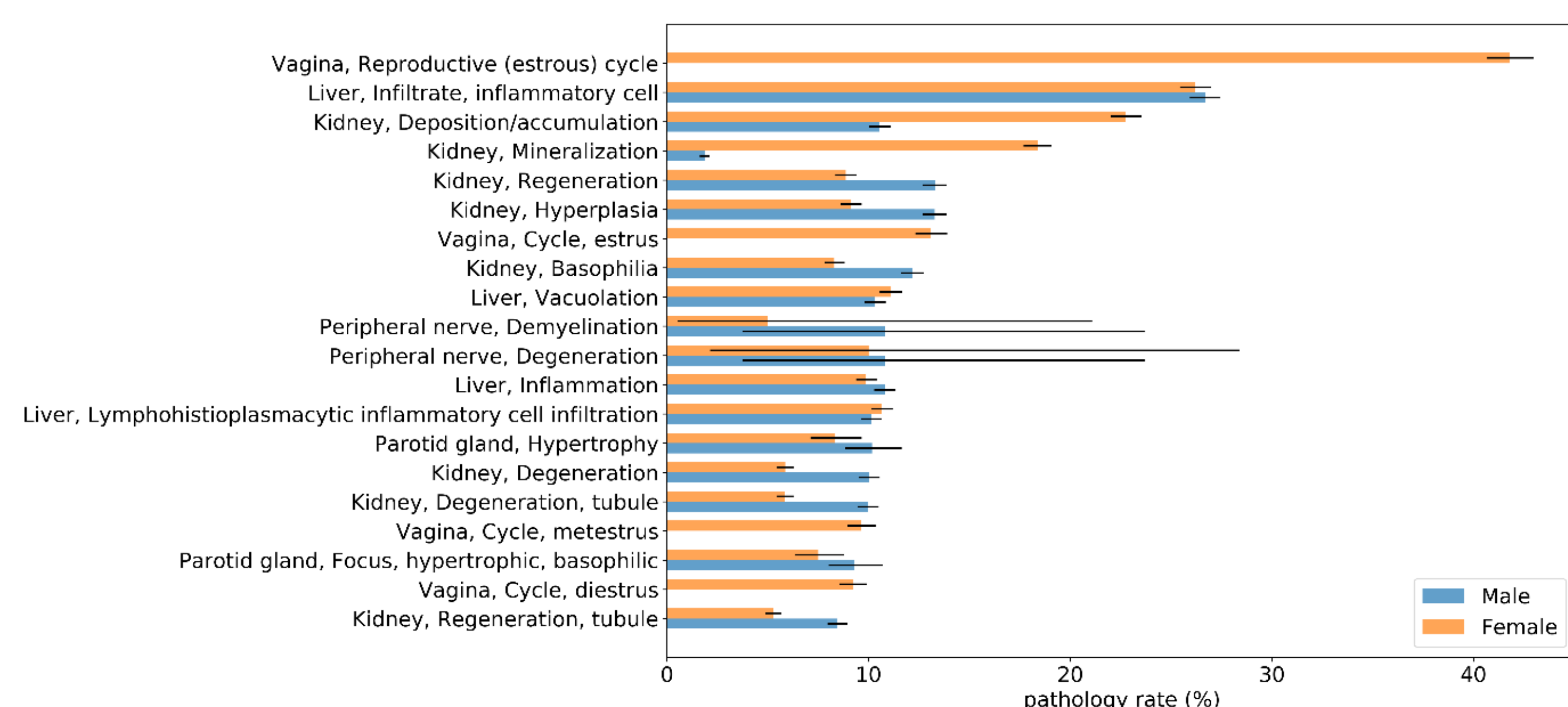
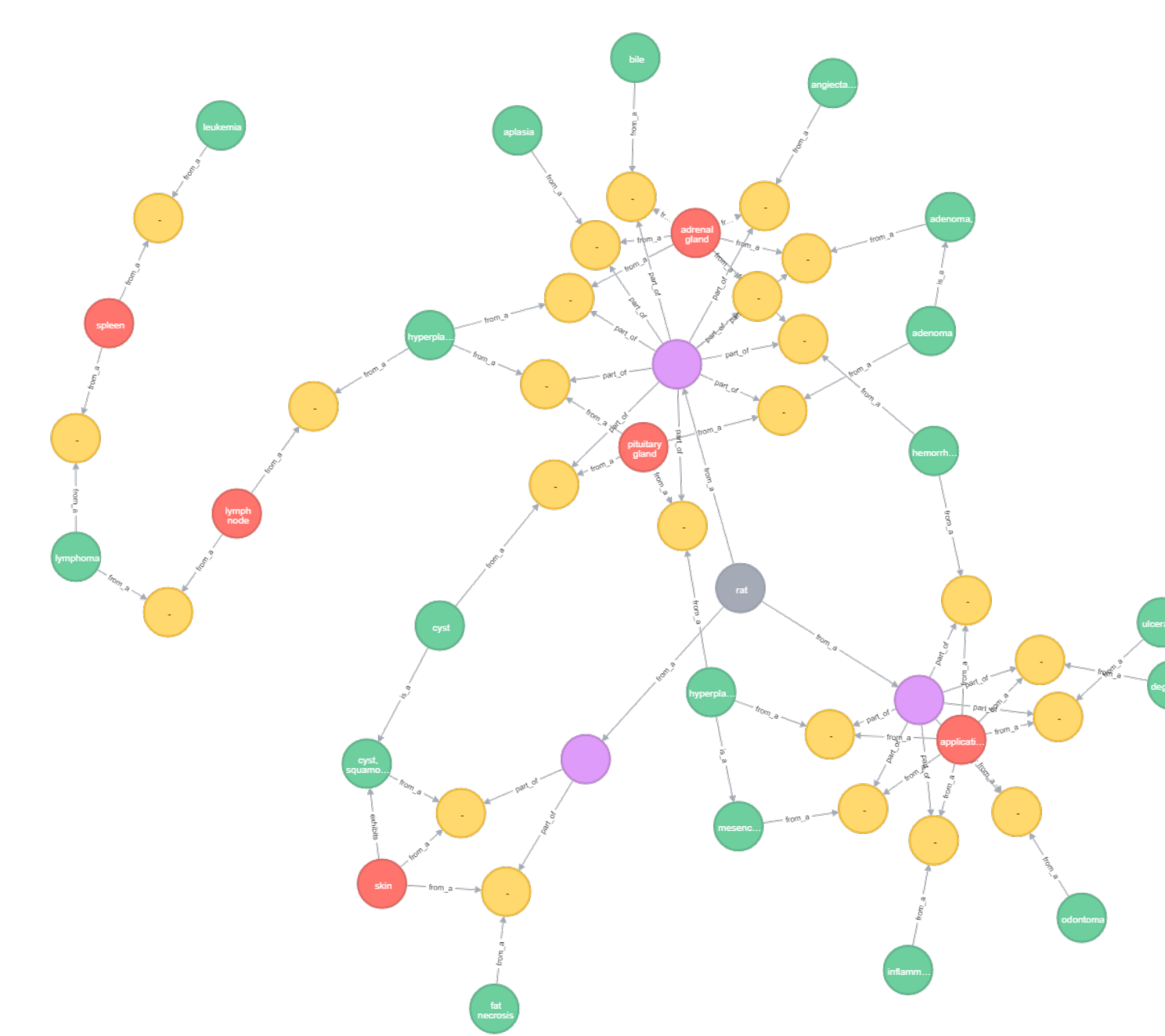
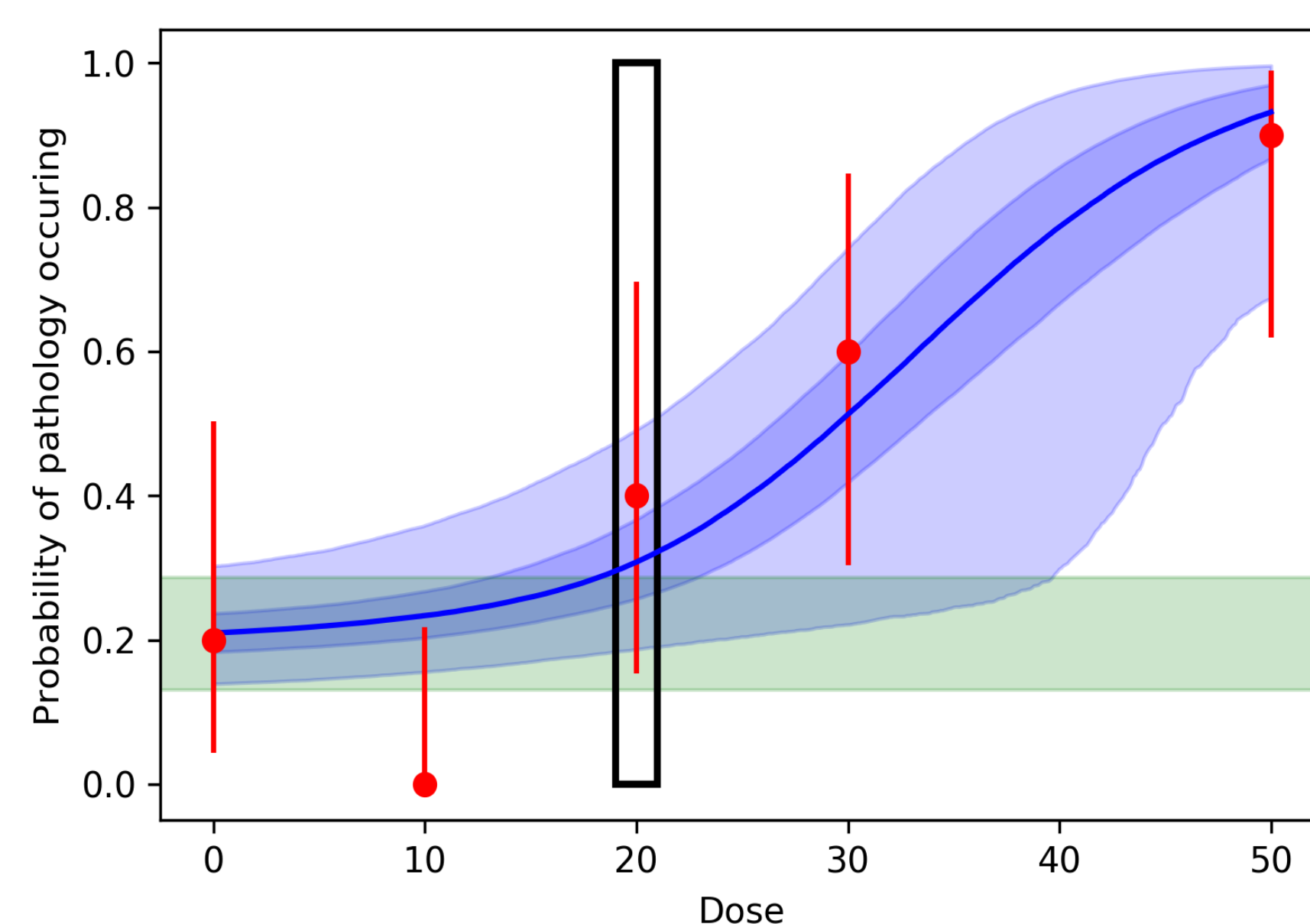
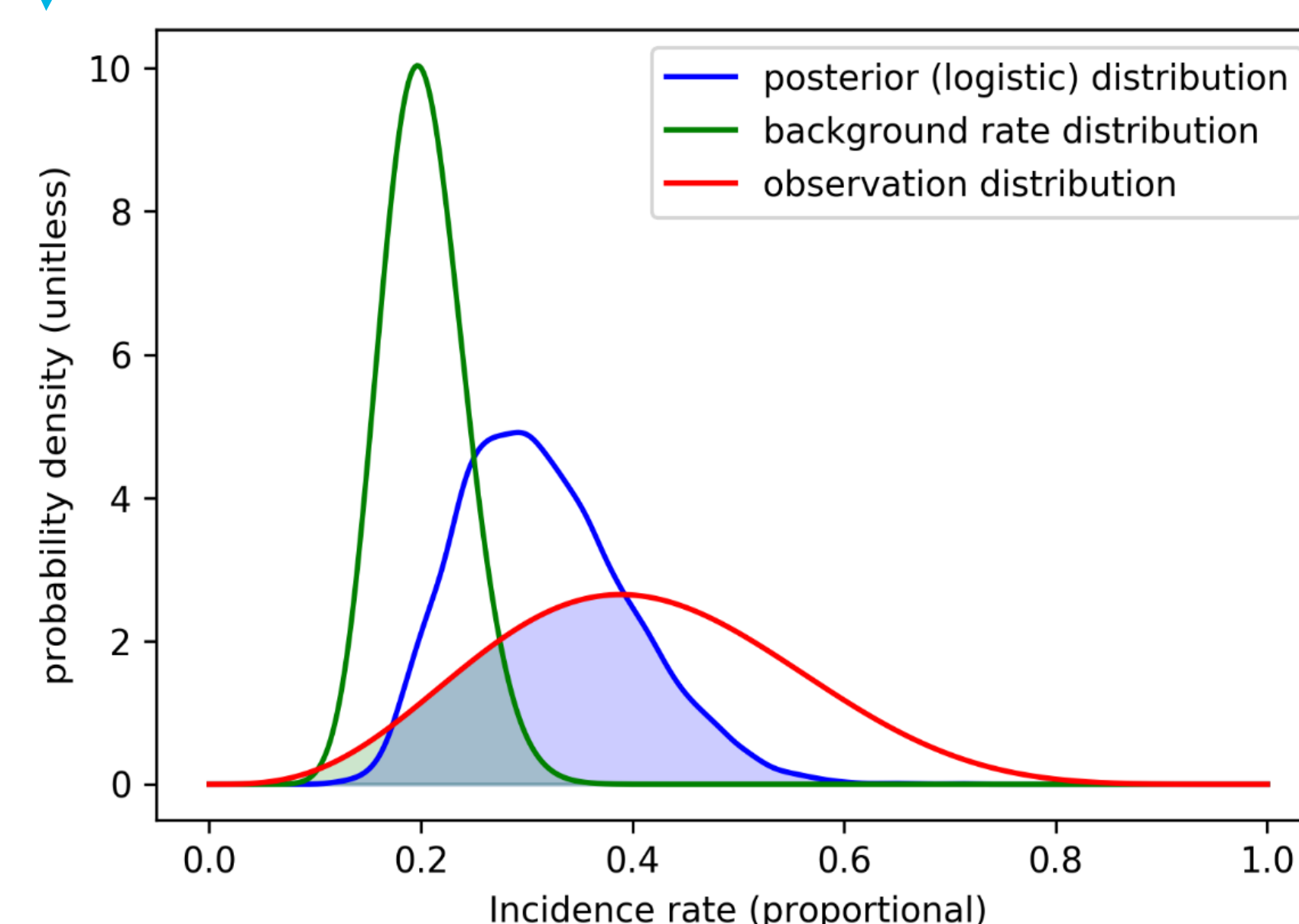
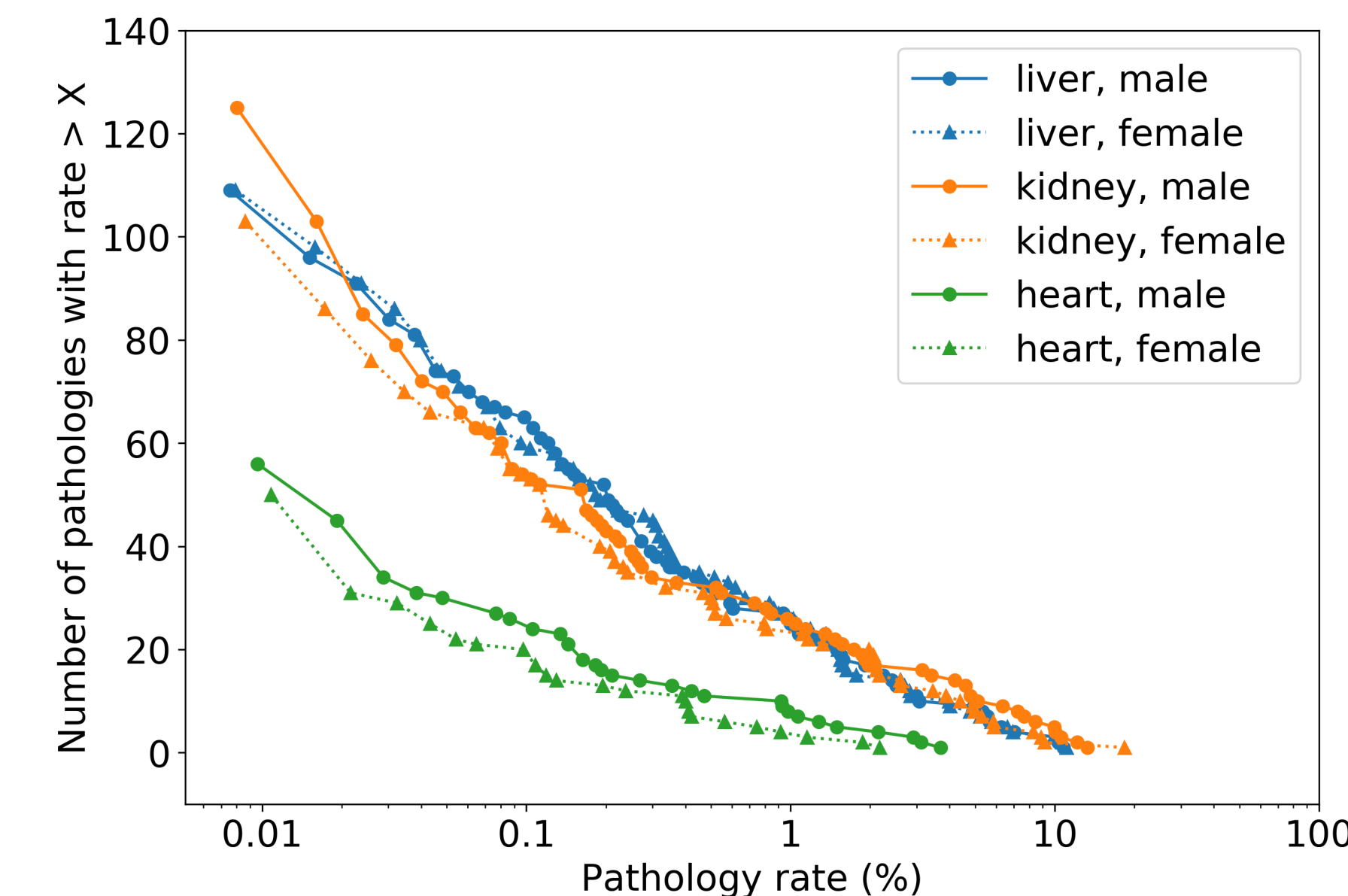
Reference interval calculation: The left hand figure shows an example population composed of a normal “healthy” distribution and log-normal increased distribution. The vertical line shows the cut-off where the result is most likely to be increased. The right hand figure shows the distribution of Leukocytes from the eTOX dataset with reference intervals calculated using 3 different methods.

Clinical pathology reference intervals

- Clinical pathology data was grouped by species, sex, and strain.
- For each group and parameter a mixture of “healthy” values, increased values and decreased values were observed.
- For each parameter a mixture model was developed. Healthy values were treated as normally distributed, while increased and decreased values were treated as log-normal.
- Given these underlying distributions, reference intervals can be calculated to identify expected values and abnormal findings.
- Abnormal findings match expert calls from the eTOX database, with ROC-AUCs of 0.92 and 0.86 for increased and decreased calls respectively.

Histopathology background rates and anomalies

- Histopathology results were standardised in line with the eTOX histopathology and organ ontologies.
- A graph database was used to allow aggregation of the data over species, sex, pathology and organ.
- Background incidence rates were calculated from multiple studies control data and can include subtypes of the queried organ or pathology, e.g., “liver” can include results from “liver left lobe” and “liver right lobe”.
- A Bayesian dose-response model was developed that allows dose dependent trends to be calculated in the presence of a known background rate.
- Abnormal findings, adverse effect levels and point-of-departures can be automatically identified by analysis of the findings, dose dependent trends, and background incidence rates.
- Abnormal findings show good agreement with expert treatment-related calls from the eTOX database (ROC-AUC = 0.84).



Top left: The background incidence rates of the 20 most common pathologies in rats (error bars show 95% confidence) calculated from all control animals. **Top right:** Example of the graph-database structure allowing background rate calculation. **Bottom left:** A Bayesian dose-response model fitted to example data, observed rates are in red, the background rate is in green, and the logistic in blue (shaded regions show median, 50% interval, and 95% interval). **Bottom middle:** Distributions from the logistic model at dose = 20. The probability of abnormality is calculated from the likelihood of the observation being from the background (shaded green), dose-response model (shaded blue), and the difference between the distributions. **Bottom right:** The distribution of background rates for all pathologies in the liver, kidney, and heart, in rats. Each point represents the number of pathologies observed in an organ with a background rate greater than X%.



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