

## **A Maximum Likelihood estimator of a Markov model for disease activity in chronic diseases that alternate between relapse and remission, for annually aggregated partial observations.**

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### **Background**

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases that have a remitting, relapsing nature. Relapses are treated with drugs or surgery. No drug can be considered a curative treatment. In CD, surgery is not curative, and may need to be performed many times, since the disease may reappear. For UC, curative surgery is possible after which it cannot relapse again.

We needed a discrete-time Markov model for the disease activity of relapse and remission with a cycle length of one month, in order to study the effect of shortening or post-poning relapses. Our data consisted of yearly observations of the individual patients. Each year, the number of relapses and surgical operations were recorded. There were no data on the time points at which relapses started or ended.

### **Method**

The disease activity model is a Markov chain with four states: 1) first month of remission, 2) subsequent months of remission, 3) first month of relapse, and 4) subsequent months of relapse. A period of remission is defined as an unbroken sequence of cycles spent in states 1 and/or 2. A relapse is defined as an unbroken sequence of cycles spent in state 3 and/or 4. Surgery can occur in states 3 and 4.

An exact maximum likelihood estimator was used, that translated the yearly observations into monthly probabilities of transition between remission and relapse, and surgery. The probability of remission depends on time since start of relapse, as does the probability of relapse since the start of remission, due to the model structure. The parameters themselves do not change over time in our context.

The initial implementation of the estimator was slow, counting through all possible pathways of the model. Many paths have a zero likelihood, and not all are unique in how their likelihood depend on the parameters. We created a list of *profiles*, with the values necessary to evaluate the likelihood of each unique pathway, given the parameter values. We thus optimized our estimator.

### **Results**

The maximum likelihood estimator appears to work well. Simulated training datasets result in reasonable estimates. The estimator initially took over three hours to complete. Optimization reduced this time to around one minute.

The estimated disease activity model fits well to observed data and has good face validity, in the absence of curative surgery. Presence of curative surgery imposes a transient nature to the disease which makes the disease activity model unsuitable.

### **Conclusions**

The disease activity model and its estimator work well. Presence of curative surgery calls for further development of the model, the estimator and its use of profiles.