Bayesian modelling to predict the evolution of eczema severity

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Introduction

Atopic Dermatitis (AD), also called eczema, is a most common chronic **skin disease** characterised by a dry, itchy skin. Given the large variation in responses to treatment from one individual to another, it is of high clinical relevance to **design personalised treatment strategies** for AD rather than using a one-size-fits-all therapy. Better **prognoses** of the course of AD severity could help choose appropriate treatment for each patient and reduce the daily fluctuation of AD symptoms (flare-up) and its impact on the quality of life.
Predictive tools should ideally be **interpretable** to be accepted by clinicians, patients and meet existing regulations (e.g. GDPR). This could be achieved with prognoses based on a **mechanistic understanding** of AD pathogenesis ("double-switch model") [1].

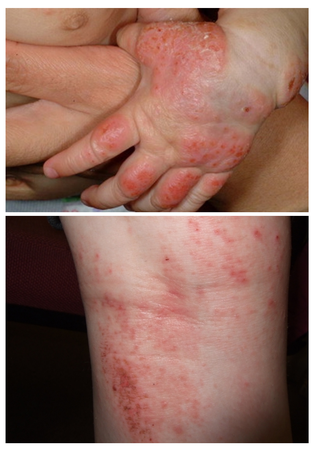

Figure 1: Eczema lesions

Objective

Develop a predictive, mechanism-based model of the short-term evolution of eczema severity.

Methods

Data [2]: Model development

- **60 children** with moderate/severe AD
- 6-9 months follow-up
- Daily "bother" & "scratch" scores (0-10)
- Corticosteroid therapy
- 30% missing values

Data [3]: External validation

- **334 children** with moderate/severe AD
- 16 weeks follow-up
- Daily "bother" score (0-10)
- Corticosteroid therapy
- 2% missing values

Model

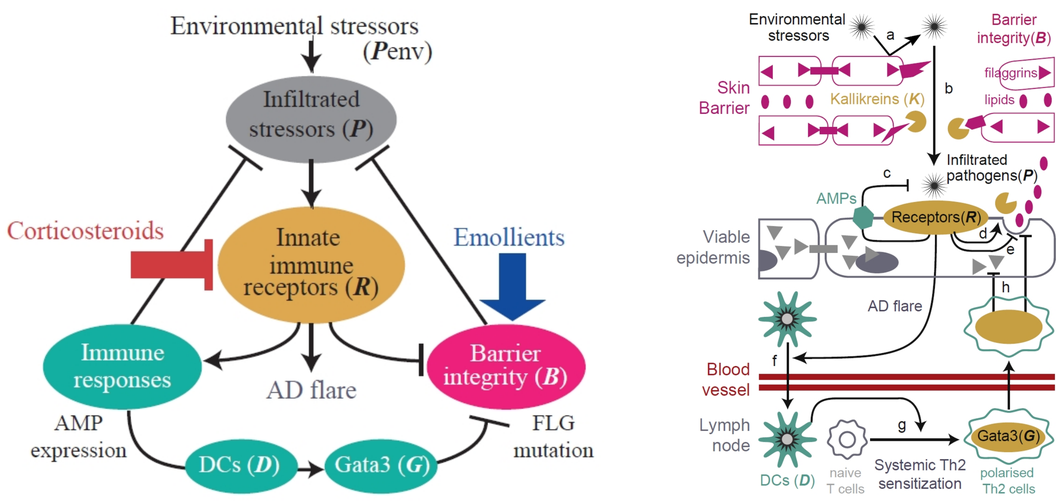

Figure 2: Double-Switch model

The double-switch model is specified as a graphical model, more specifically a **Bayesian network**. The parameters of the model θ (probability distributions) are updated with Bayes's theorem when data x is observed:

$$p(\theta|x) = \frac{p(x|\theta)p(\theta)}{p(x)} \tag{1}$$

Inference is performed with the Hamiltonian Monte-Carlo (MCMC) using the probabilistic programming language Stan.

For i indexing patients, k days; with $\boldsymbol{D}$ the observed severity score (bother or scratch), $\boldsymbol{C}$ the treatment, R a latent flare-up and P a latent risk; the model is defined by (priors not shown):

$$\begin{cases} \boldsymbol{D}_i(k+1) \sim \mathcal{N}\Big(w_{D_i} \cdot \boldsymbol{D}_i(k) + w_{C_i} \cdot \boldsymbol{C}_i(k) + R_i(k) + b_D, \sigma_D^2\Big) \\ w_{C_i} \sim \mathcal{N}(\mu_{w_C}, \sigma_{w_C}^2) \\ R_i(k) \sim \text{Exp}(\beta = P_i(k)) \\ \log\Big(P_i(k+1)\Big) \sim \mathcal{N}\Big(\log\Big(P_i(k)\Big), \sigma_P^2\Big) \end{cases} \tag{2}$$

Missing scores are treated as random variables in a **semi-supervised** setting.

Predictions are **calibrated** using pairwise "one-against-all" isotonic regressions.

Performance evaluation

- To make sure the model generalises well to unseen data, it is tested in a **forward chaining** setting (see figure 3).
- Predictions are evaluated using the **Ranked Probability Skill Score** (RPSS) and **calibration curves**. The RPSS measures the accuracy of an ordinal probabilistic forecast (0: chance-level, 1: perfect).

Results

Internal validation

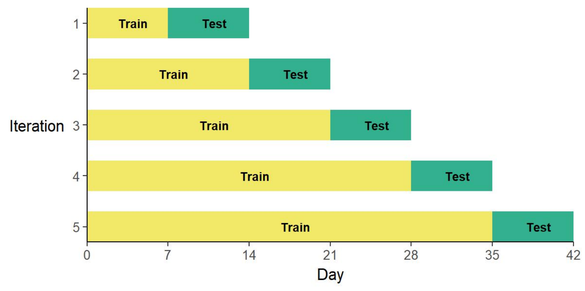

Figure 3: Forward Chaining

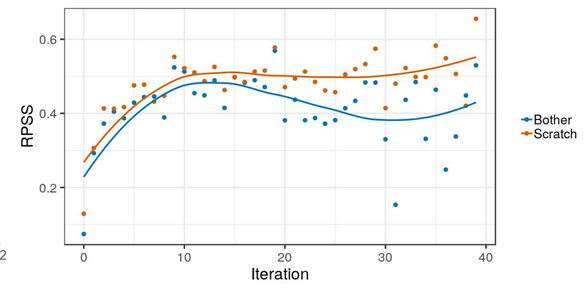

Figure 4: Learning curve

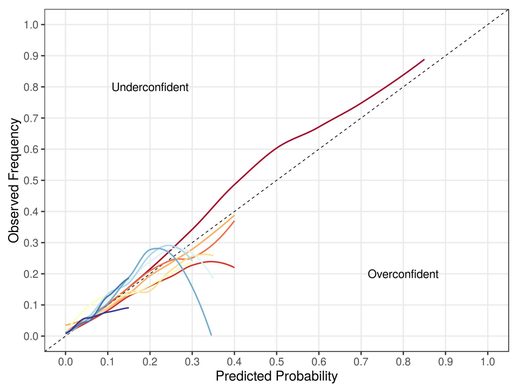

Figure 5: Calibration curve for bother

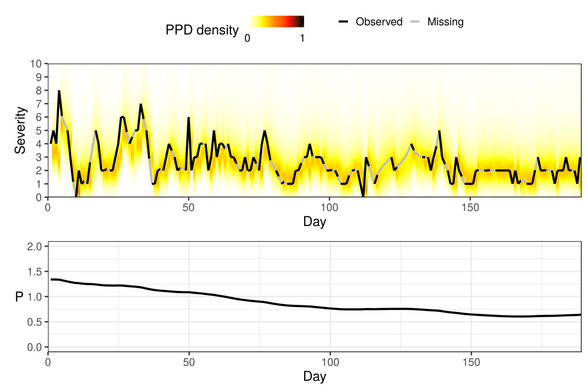

Figure 6: Patient #1 trajectory and prediction

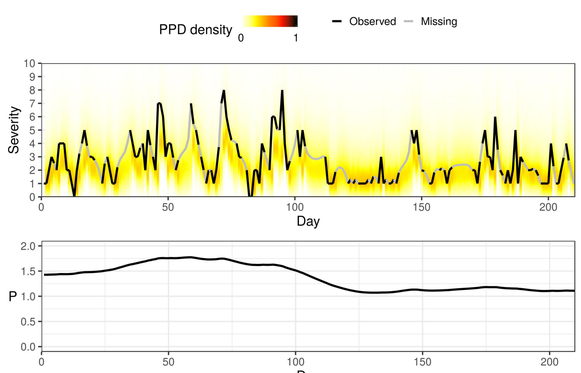

Figure 7: Patient #2 trajectory and prediction

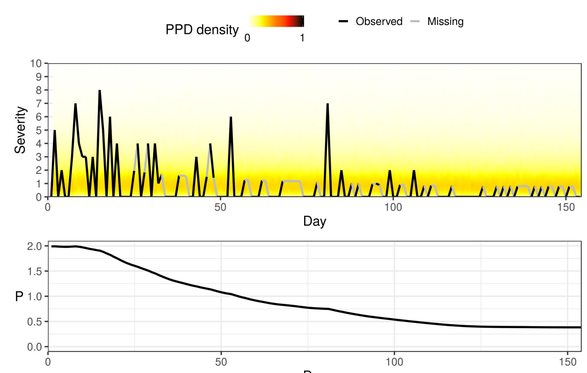

Figure 8: Patient #3 trajectory and prediction

External validation

Using data [3], the **RPSS is increased to 60%** (vs 50% with data [2]) confirming the generalisability of the model.

Toward optimal control

The model was extended to **account for the quantity and type of treatment** used (mild, moderate, potent and very potent topical steroids or calcineurin inhibitors; "step-up") **and patient information** (filaggrin mutation, ethnicity, sex, age).

- Fillagrin mutation was associated with lower improvement
- 64/327 patients had a significant positive response to topical steroids
- 29/327 patients had a significant positive response to step-up
- 4/327 patients had a significant positive response to calcineurin inhibitors

Conclusion

- We developed and validated a mechanism-based model of the evolution of AD with two datasets.
- Predictions are 50% to 60% better than chance
- A Sequential Monte-Carlo algorithm will be implemented to perform online learning and to be included in a Reinforcement Learning setting.

Acknowledgements

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References

[1] E. Domínguez-Hüttinger, P. Christodoulides, K. Miyauchi, A. D. Irvine, M. Okada-Hatakeyama, M. Kubo, and R. J. Tanaka, ``Mathematical modeling of atopic dermatitis reveals “double-switch” mechanisms underlying 4 common disease phenotypes,'' *Journal of Allergy and Clinical Immunology*, vol. 139, no. 6, pp. 1861--1872, 2017.

[2] S. M. Langan, P. Silcocks, and H. C. Williams, ``What causes flares of eczema in children?,'' *British Journal of Dermatology*, vol. 161, no. 3, pp. 640--646, 2009.

[3] K. S. Thomas and T. H. Sach, ``A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: Protocol for the Softened Water Eczema Trial (SWET) (ISRCTN: 71423189),'' *British Journal of Dermatology*, vol. 159, pp. 561--566, 6 2008.