

PyNM: a Lightweight Python implementation of Normative Modeling

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Summary

The majority of studies in neuroimaging and psychiatry are focussed on case-control analysis ([Marquand et al., 2019](#)). However, case-control relies on well-defined groups which is more the exception than the rule in biology. Psychiatric conditions are diagnosed based on symptoms alone, which makes for heterogeneity at the biological level ([Marquand et al., 2016](#)). Relying on mean differences obscures this heterogeneity and the resulting loss of information can produce unreliable results or misleading conclusions ([Loth et al., 2021](#)).

Normative Modeling is an emerging alternative to case-control analyses that seeks to parse heterogeneity by looking at how individuals deviate from the normal trajectory. Analogous to normative growth charts, normative models map the mean and variance of a trait for a given population against a set of explanatory variables (usually including age). Statistical inferences at the level of the individual participant can then be obtained with respect to the normative range ([Marquand et al., 2019](#)). This framework can detect patterns of abnormality that might not be consistent across the population, and recasts disease as an extreme deviation from the normal range rather than a separate group.

PyNM is a lightweight python implementation of Normative Modeling making it approachable and easy to adopt. The package provides:

- Python API and a command-line interface for wide accessibility
- Automatic dataset splitting and cross-validation
- Five models from various back-ends in a unified interface that cover a broad range of common use cases
- Solutions for very large datasets and heteroskedastic data
- Integrated plotting and evaluation functions to quickly check the validity of the model fit and results
- Comprehensive and interactive tutorials

Statement of need

The basic idea underpinning Normative Modeling is to fit a model on the controls (or a subset of them) of a dataset, and then apply it to the rest of the participants. The difference between the model's prediction and the ground truth for the unseen participants relative to the variance around the prediction quantifies their deviation from the normal. While simple in concept, implementing Normative Modeling requires some care in managing the dataset and choosing an appropriate model.

In principle, any model that estimates both the mean and variance of the predictive distribution could be used for Normative Modeling. However, in practice, we impose more constraints.

First and foremost, the assumptions of the model must be met by the data. Second, it is important to distinguish between epistemic and aleatoric uncertainty. Epistemic or systematic uncertainty stems from how information about the distribution is collected, whereas aleatoric uncertainty is intrinsic to the distribution and represents the true variation of the population ([Xu et al., 2021](#)).

To the author's knowledge, PCNtoolkit ([Marquand et al., 2021](#)) is the only other available package for Normative Modeling. It implements methods that have been applied in a range of psychiatry and neuroimaging studies ([Fraza et al., 2021; Kia et al., 2020, 2021; Rutherford, Fraza, et al., 2022](#)), and is accompanied by thorough [tutorials](#), a [forum](#), and a framework for Normative Modeling in computational psychiatry ([Rutherford, Kia, et al., 2022](#)). While PCNtoolkit offers more advanced functionality, PyNM emphasizes being lightweight and easy to use, and implements different models than PCNtoolkit including a wrapper for the GAMLSS package from R, which is a powerful option for Normative Modeling ([Dinga et al., 2021](#)).

PyNM is intended to take users from their first steps in Normative Modeling to using advanced models on complex datasets. Crucially, it manages the dataset and has interactive tutorials – making it quick for new users to try the method either on their own data or on provided simulated data. The tutorials motivate the use of each model and highlight their limitations to help clarify which model is appropriate for what data, and built-in plotting and evaluation functions ([Figure 1](#)) make it simple to check the validity of the model output. The package includes five models from various backends in a unified interface, including a wrapper for GAMLSS ([Rigby & Stasinopoulos, 2005](#)) from R that is otherwise not yet available in python, and the selected models cover many settings including big data and heteroskedasticity.

Earlier versions of PyNM code were used in the following publications:

- Lefebvre et al. ([2018](#))
- Maruani et al. ([2019](#))
- Bethlehem et al. ([2020](#))

Usage Example

```
from pynn.pynn import PyNM

# Load data
# df contains columns 'score','group','age','sex','site'
df = pd.read_csv('data.csv')

# Initialize pynn w/ data and confounds
m = PyNM(df,'score','group', confounds = ['age','c(sex)','c(site')'])

# Run models
m.loess_normative_model()
m.centiles_normative_model()
m.gp_normative_model()
m.gamlss_normative_model()

# Collect output
data = m.data
```

Figures

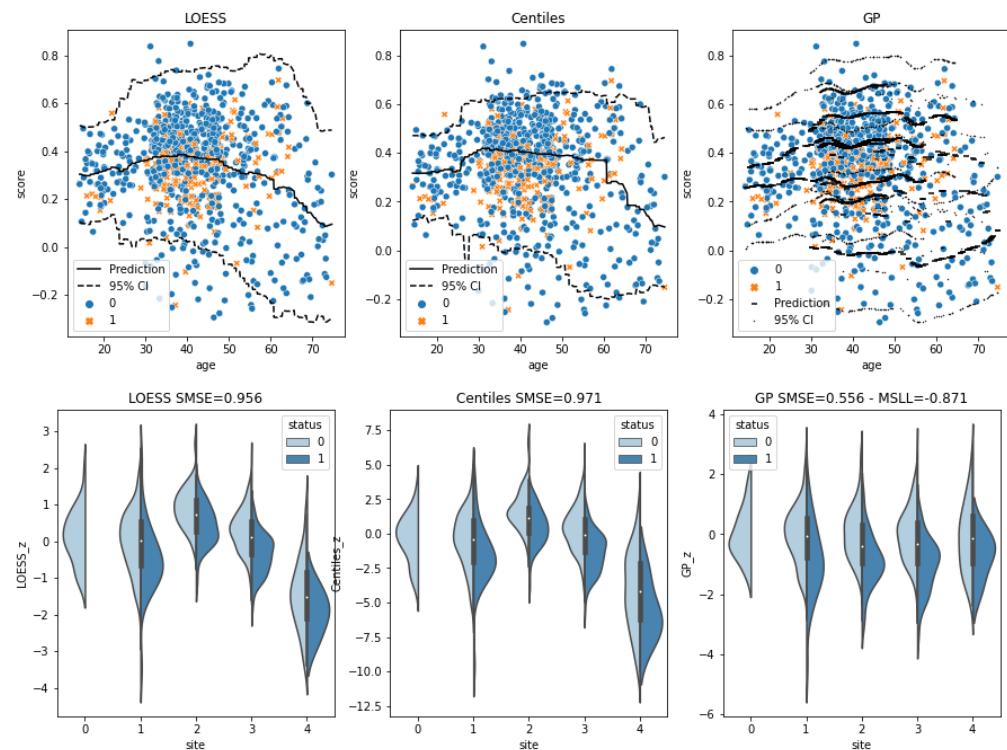


Figure 1: Output of built-in plotting function for model fit and residuals.

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References

- Bethlehem, R. A. I., Seidlitz, J., Romero-Garcia, R., Trakoshis, S., Dumas, G., & Lombardo, M. V. (2020). A normative modelling approach reveals age-atypical cortical thickness in a subgroup of males with autism spectrum disorder. *Communications Biology*, 3(1), 486. <https://doi.org/10.1038/s42003-020-01212-9>
- Dinga, R., Fraza, C. J., Bayer, J. M. M., Kia, S. M., Beckmann, C. F., & Marquand, A. F. (2021). Normative modeling of neuroimaging data using generalized additive models of location scale and shape. *bioRxiv*. <https://doi.org/10.1101/2021.06.14.448106>
- Fraza, C. J., Dinga, R., Beckmann, C. F., & Marquand, A. F. (2021). Warped bayesian linear regression for normative modelling of big data. *NeuroImage*, 245, 118715. <https://doi.org/10.1016/j.neuroimage.2021.118715>
- Kia, S. M., Huijsdens, H., Dinga, R., Wolfers, T., Mennes, M., Andreassen, O. A., Westlye, L. T., Beckmann, C. F., & Marquand, A. F. (2020). Hierarchical bayesian regression for

- multi-site normative modeling of neuroimaging data. In A. L. Martel, P. Abolmaesumi, D. Stoyanov, D. Mateus, M. A. Zuluaga, S. K. Zhou, D. Racoceanu, & L. Joskowicz (Eds.), *Medical image computing and computer assisted intervention – MICCAI 2020* (pp. 699–709). Springer International Publishing. ISBN: 978-3-030-59728-3
- Kia, S. M., Huijdsens, H., Rutherford, S., Dinga, R., Wolfers, T., Mennes, M., Andreassen, O. A., Westlye, L. T., Beckmann, C. F., & Marquand, A. F. (2021). Federated multi-site normative modeling using hierarchical bayesian regression. *bioRxiv*. <https://doi.org/10.1101/2021.05.28.446120>
- Lefebvre, A., Delorme, R., Delanoë, C., Amsellem, F., Beggiato, A., Germanaud, D., Bourgeron, T., Toro, R., & Dumas, G. (2018). Alpha waves as a biomarker of autism spectrum disorder: The challenge of reproducibility and heterogeneity. *Frontiers in Neuroscience*, 12. <https://doi.org/10.3389/fnins.2018.00662>
- Loth, E., Ahmad, J., Chatham, C., López, B., Carter, B., Crawley, D., Oakley, B., Hayward, H., Cooke, J., San José Cáceres, A., Bzdok, D., Jones, E., Charman, T., Beckmann, C., Bourgeron, T., Toro, R., Buitelaar, J., Murphy, D., & Dumas, G. (2021). The meaning of significant mean group differences for biomarker discovery. *PLOS Computational Biology*, 17(11), 1–16. <https://doi.org/10.1371/journal.pcbi.1009477>
- Marquand, A. F., Kia, S. M., Zabihi, M., Wolfers, T., Buitelaar, J. K., & Beckmann, C. F. (2019). Conceptualizing mental disorders as deviations from normative functioning. *Molecular Psychiatry*, 24(10), 1415–1424. <https://doi.org/10.1038/s41380-019-0441-1>
- Marquand, A. F., Rezek, I., Buitelaar, J., & Beckmann, C. F. (2016). Understanding heterogeneity in clinical cohorts using normative models: Beyond case-control studies. *Biological Psychiatry*, 80(7), 552–561. <https://doi.org/10.1016/j.biopsych.2015.12.023>
- Marquand, A. F., Rutherford, S., Kia, S. M., Wolfers, T., Fraza, C., Dinga, R., & Zabihi, M. (2021). *PCN Toolkit (0.20)*. Zenodo. <https://doi.org/10.5281/zenodo.5207839>
- Maruani, A., Dumas, G., Beggiato, A., Traut, N., Peyre, H., Cohen-Freoua, A., Amsellem, F., Elmaleh, M., Germanaud, D., Launay, J.-M., Bourgeron, T., Toro, R., & Delorme, R. (2019). Morning plasma melatonin differences in autism: Beyond the impact of pineal gland volume. *Frontiers in Psychiatry*, 10. <https://doi.org/10.3389/fpsyg.2019.00011>
- Rigby, R. A., & Stasinopoulos, D. M. (2005). Generalized additive models for location, scale and shape. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 54(3), 507–554. <https://doi.org/10.1111/j.1467-9876.2005.00510.x>
- Rutherford, S., Fraza, C., Dinga, R., Kia, S. M., Wolfers, T., Zabihi, M., Berthet, P., Worker, A., Verdi, S., Andrews, D., Han, L. K., Bayer, J. M., Dazzan, P., McGuire, P., Mocking, R. T., Schene, A., Sripatha, C., Tso, I. F., Duval, E. R., ... Marquand, A. F. (2022). Charting brain growth and aging at high spatial precision. *eLife*, 11, e72904. <https://doi.org/10.7554/eLife.72904>
- Rutherford, S., Kia, S. M., Wolfers, T., Fraza, C., Zabihi, M., Dinga, R., Berthet, P., Worker, A., Verdi, S., Ruhe, H. G., Beckmann, C. F., & Marquand, A. F. (2022). The normative modeling framework for computational psychiatry. *Nature Protocols*, 17(7), 1711–1734. <https://doi.org/10.1038/s41596-022-00696-5>
- Xu, B., Kuplicki, R., Sen, S., & Paulus, M. P. (2021). The pitfalls of using gaussian process regression for normative modeling. *PLOS ONE*, 16(9), 1–14. <https://doi.org/10.1371/journal.pone.0252108>