



DINAMIC

EXPLORATORY  
PROJECT

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**Coordination**

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Mixed-type data

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Copulas

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**Participating INRAE units**

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[Transfrontalière BioEcoAgro](#)

[GQE-Le Moulon](#)

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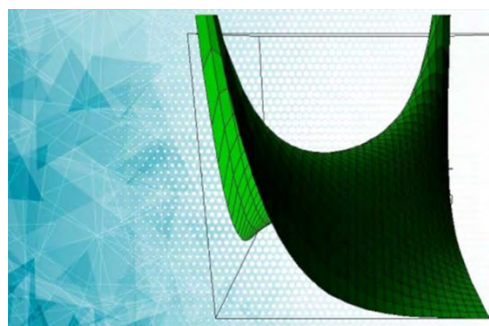
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## Understanding the plasticity of complex biological networks using copula models



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### Context, key challenges and goals

The study of a biological system requires the acquisition of a large quantity of data of different kinds (measurements, counts, absence/presence, etc.). The resultant 'mixed-type' datasets are not easily handled by the mathematical tools traditionally used by biologists and analysts, causing difficulties for scientists attempting to infer biological networks, a process that involves the reconstruction of the interrelationships between the constituent elements of an organism (molecules, cells, organs) using experimental data. The problem is significant, since the inference of biological networks is a much-needed task in various areas of research, not only allowing a better understanding of the organisms under investigation, but also enabling the study of their plasticity, that is, their ability to respond to phenotypical, environmental and introduced variations. There is thus a very real need for tools that can effectively support the inference of networks.



Parametric 'copula' models show particular promise in this context. Copulas are mathematical tools that can establish relationships between data of disparate natures. The challenge for the DINAMIC project was therefore to develop a copula model in graphical form that would *also* be computationally effective.

The DINAMIC project brought together a group of INRAE units to develop and implement a multivariate copula-based model that could be applied to the differential analysis of mixed-type networks. This innovative model had the distinction of being applicable to varied domains.

## Outcomes

### **Proof of concept: use of differential network analysis tools for data processing**

Network inference tools already developed in the literature were employed to explore the characteristics of three datasets acquired in previous INRAE projects in the areas of human health, the genomics of maize and the genomics of bulls. The analysis performed by the DINAMIC project enabled concrete conclusions to be drawn in these three domains, demonstrating the usefulness of this type of analytical approach. The analysis of the genomics of cattle was used, for example, in the development of an epigenotyping chip (RUMIGEN project). The results obtained by the three projects will be compared with the results from copula-based models.

Additional data were also obtained from the maize and cattle genomics projects to enable further analysis to be conducted that will expand knowledge in these areas of investigation and lay the groundwork for future biological validation.

### **Methodological, computational and theoretical advances in copula-based modelling**

The project leaders developed a method that made network inferencing possible for complex multivariate models. The generic method is applicable to many models, including copula models. It was applied, in particular, to multivariate count data from a study on the transcriptome of a bee parasite and the transcriptome's variation across the parasite's life cycles. The approach, which uses a Gaussian copula, was also integrated into *rpl* and *heterocop* R packages. Last, two Masters projects concentrated specifically on the use of Gaussian copula models for the processing of mixed-type data (using the data collected from cattle), providing a proof of concept and leading to the production of two research papers.

## Future directions

### **An enthusiastic community that hopes to continue its work**



The DINAMIC project brought together seven INRAE units across five different research divisions and established the basis for a new partnership with CIRAD. Solid methodological advances were achieved, but a number of problems have still to be resolved before copula models are ready to use in the processing of mixed-type data sets. Exploration of these problems will continue, not only via the several actions made possible directly by the project's results to date, but also as the result of the keen engagement generated by the project, which has built a truly enthusiastic multidisciplinary community eager to use copula models for the inference of biological networks. The actions resulting from the project are varied:

- Funding for Ekaterina Tomilina's thesis (2022-2025, joint funding from DIGIT-BIO and EDHD) on the development of theoretical and methodological tools for the use of copula models to process multi-omics data;
- Supplementary funding for Amrita Raja-Rai-Shankar's thesis (2023-2026) which uses, in particular, the methylation data collected by DINAMIC;
- The ANR-funded ExoNutriAge JCJC project (2024-2027), led by Jean-Christophe Delpech, on the analysis of extracellular vesicles<sup>1</sup> extracted from the blood samples taken in the earlier project on human health, which includes the use of analytical methods developed by DINAMIC;
- The ADAAPT project (2024-2028, Agroecology and Digital Technologies PEPR) led by Laurence Drouilhet, which predominantly makes use of the epigenotyping chip and which will be able to benefit from the tools and methods developed by DINAMIC.

<sup>1</sup> Sac-like structures naturally secreted by cells, that contain and transport various materials from the cells (proteins, RNA, metabolites).

## Publications

- Gildas Mazo, Dimitris Karlis, Andrea Rau. A randomized pairwise likelihood method for complex statistical inferences, Journal of the American Statistical Association, 2023, 119 (547), p 2317-2327 [10.1080/01621459.2023.2257367](https://doi.org/10.1080/01621459.2023.2257367), [hal-03126620](https://hal.inrae.fr/hal-03126620)
- Delpech, J.-C., Yeh, H., Kalavai, S. V., You, Y., Ruan, Z., Touch, N., Hersh, S., Monguillon, P., Johnson, W. E., Rau, A., Madore, C., Ikezu, T. and Ikezu, S. Sex specific correction of maternal inflammation-induced behavioral abnormalities by the inhibition of colony-stimulating factor 1 receptor, Brain Behavior and Immunity, 2025, 131:106163, <https://doi.org/10.1016/j.bbi.2025.106163>.
- Tomilina, E., Jaffrézic, F., Mazo, G. Gaussian copula correlation network analysis of mixed-type data using a semi-parametric pairwise likelihood with a multi-omics application, Computational Statistics & Data Analysis, 2026, 223:108414, <https://doi.org/10.1016/j.csda.2026.108414>, <https://hal.inrae.fr/hal-04847648v4/>

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