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Encoding of neural networks of different architectures to SBML format

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Despite advancements in Systems Biology, developing purely ODE-based mechanistic models remains challenging due to incomplete knowledge of parameters or computational inefficiencies. In such cases, hybrid and data-driven approaches provide viable alternatives. To facilitate seamless simulation and analysis alongside classical ODE-based models, it is advantageous to encode data-driven models in the Systems Biology Markup Language (SBML).

This work presents a framework for encoding neural networks of various architectures in SBML, enabling their integration into existing computational biology tools. We implemented feed-forward and Elman recurrent neural networks (RNNs) with Tanh and ReLU activation functions. Our approach is demonstrated using two well-known case studies: (1) the *Escherichia coli* threonine synthesis model and (2) protein synthesis in a fed-batch bioreactor.

To validate our framework, we simulated the models in COPASI, a widely used tool for SBML-based simulations. While the Tanh function is natively supported in SBML, it often results in slow convergence during training. We explored the introduction of alternative activation functions, such as ReLU, via user-defined functions. Additionally, we examined the advantages of Elman RNNs over feed-forward networks, particularly for time-series modeling. Our results indicate that Elman RNNs outperform feed-forward networks in cases where data is limited and the system evolves rapidly, as observed in the bioreactor case study. Recurrence in RNNs was implemented using SBML events.

Further analysis revealed that decomposing mathematical expressions—by defining each neural network node as an SBML species or parameter—significantly reduces simulation time in COPASI compared to models where assignment rules are applied only to outputs. This effect becomes particularly pronounced in larger models. Overall, our findings highlight the feasibility of encoding neural networks in SBML, which can be useful for further development of hybrid models.

REFERENCES

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Primary authors: MOSKOVKINA, Ekaterina (NOVA School of Science and Technology, Universidade NOVA de Lisboa); PINTO, José (NOVA School of Science and Technology, Universidade NOVA de Lisboa); COSTA, Rafael (NOVA School of Science and Technology, Universidade NOVA de Lisboa); OLIVEIRA, Rui (NOVA School of Science and Technology, Universidade NOVA de Lisboa)

Presenter: MOSKOVKINA, Ekaterina (NOVA School of Science and Technology, Universidade NOVA de Lisboa)

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