# Hybrid AI - Integrating Machine Learning and Mechanistic Models: Unlocking the Potential of Hybrid Approaches

Prof. Verena Wolf

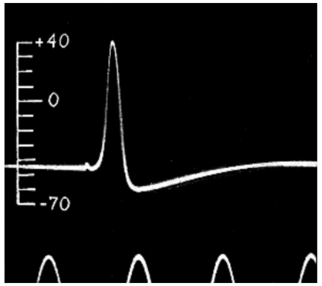
Saarland University and German Research Center for Artificial Intelligence (DFKI)

# Mechanistic Modeling

Describe mechanistic relationships by mathematical models.

- long history and key driver for scientific discoveries

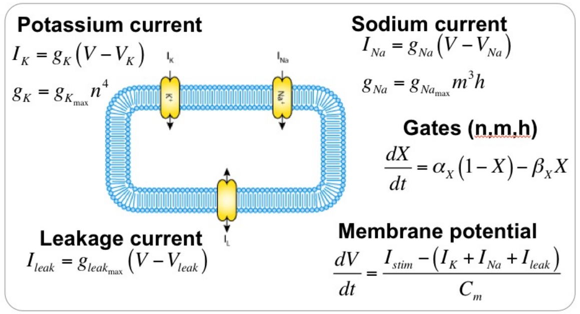
measurements of real-world system




generate hypotheses/ calibrate model

validate hypotheses/ reproduce and explain data

mechanistic model




Quelle: https://models.physiomeproject.org/

# Data-driven AI

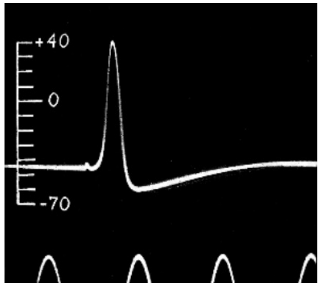
Flexible function approximation to recognize patterns in high-dim. data.

# Mechanistic Modeling

Describe mechanistic relationships by mathematical models.

- long history and key driver for scientific discoveries

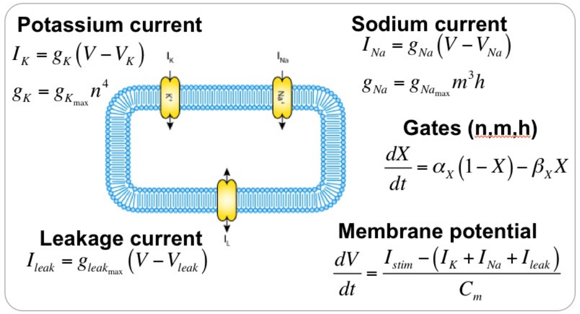
measurements of real-world system




generate hypotheses/ calibrate model

validate hypotheses/ reproduce and explain data

mechanistic model



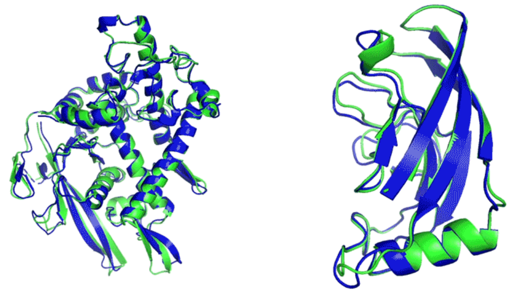

Quelle: https://models.physiomeproject.org/

# Data-driven AI

Flexible function approximation to recognize patterns in high-dim. data.

- Artificial neural networks (1950s/1960s)
- boom in the 21st century: Deep Learning

Protein Folding



T1037 / 6vr4
90.7 GDT
(RNA polymerase domain)

T1049 / 6y4f
93.3 GDT
(adhesin tip)

Experimental result
Computational prediction

Source: https://deepmind.com/

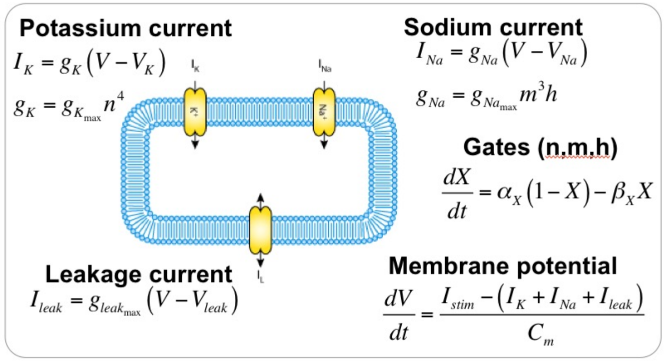
Two orthogonal approaches with different strength and weaknesses.
Can we combine them to get the best of both worlds?

mechanistic model ⟷ machine learning model/ ANN

# Mechanistic Model

describes the underlying mechanisms of a system in a quantitative manner based on hypotheses, established principles and laws.

*Hodgkin-Huxley Model 1952, Cell Excitability*

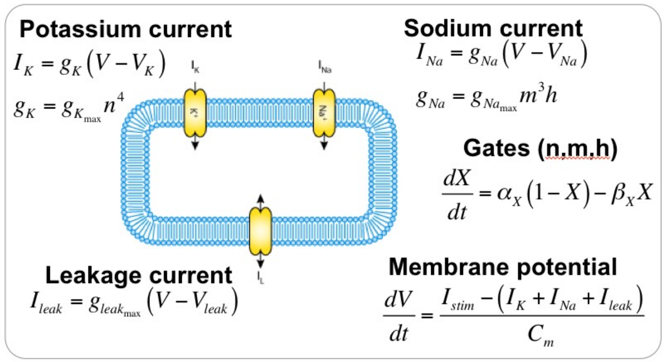



Quelle: https://models.physiomeproject.org/

# Mechanistic Model

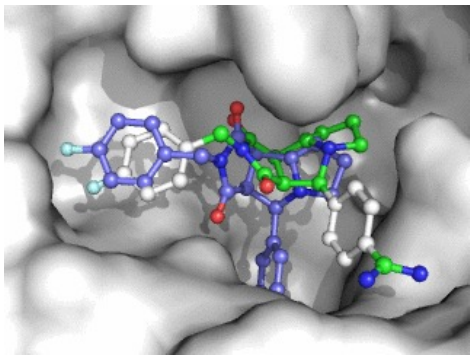
describes the underlying mechanisms of a system in a quantitative manner based on hypotheses, established principles and laws.

*Hodgkin-Huxley Model 1952, Cell Excitability*




Quelle: https://models.physiomeproject.org/

*Docking Simulation*



Quelle: https://www.compobelisk.com/

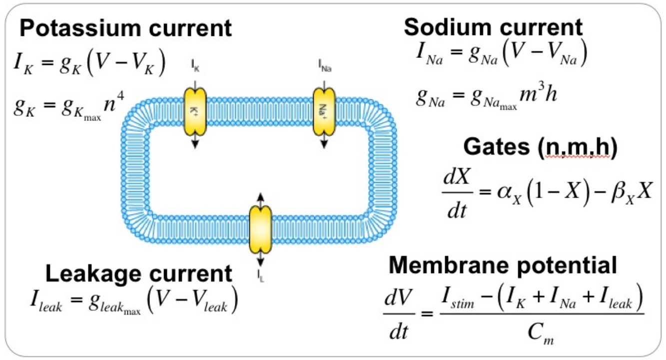
*Digital twin, automotive plant*

Quelle: https://www.faro.com/

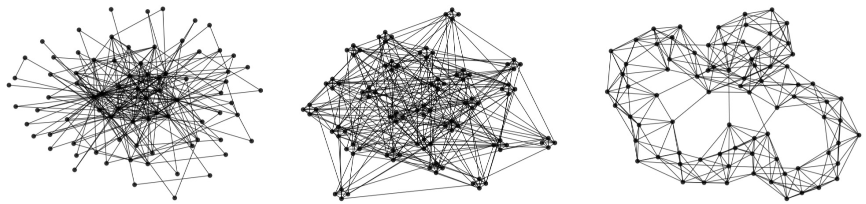
# Advantages of Mechanistic Models

- after validation: simulation of the model produces "**artificial data**" (generative/forward model)
- **reusable** for subsequent use
- **what-if simulation**: modify parameters/initial conditions, additional rules, noise, …
- **interpretable** by design
- **deductive capability** via mechanistic principles

*Hodgkin-Huxley Model 1952, Cell Excitability*



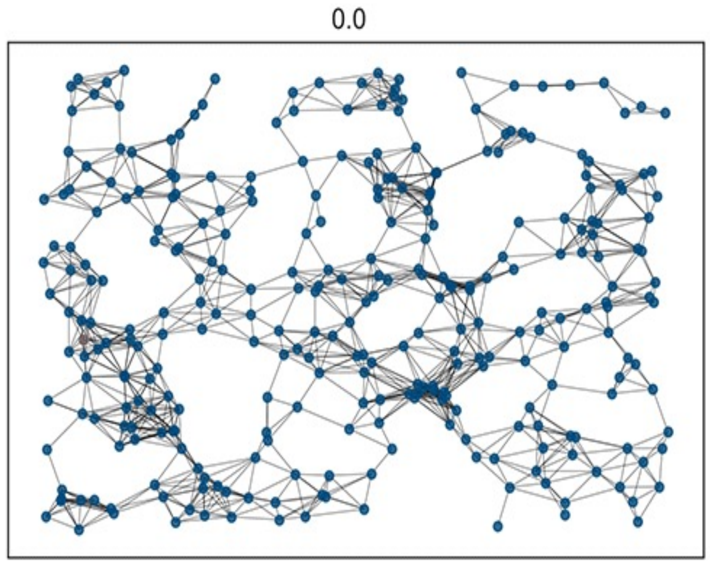
# What-If Simulation Example: Spreading Processes



Heterogeneity matters: Contact structure and individual variation shape epidemic dynamics.

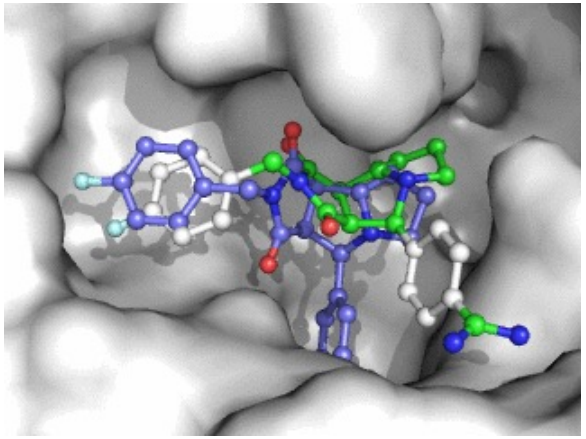
Großmann, Backenköhler, Wolf, PlosOne, 2021.

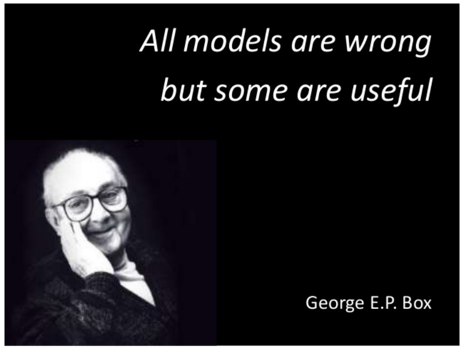
How do network characteristics and individual variation influence the spreading dynamics?
→ average number of infected individuals changes drastically over time



# Drawbacks of Mechanistic Models

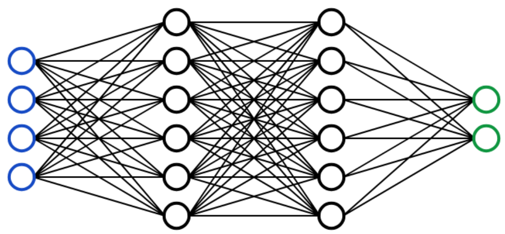
- **model complexity limited** to human-understandable rules/known laws/mechanistic understanding
- **oversimplified assumptions**
- difficult to handle **high-dimensional data**



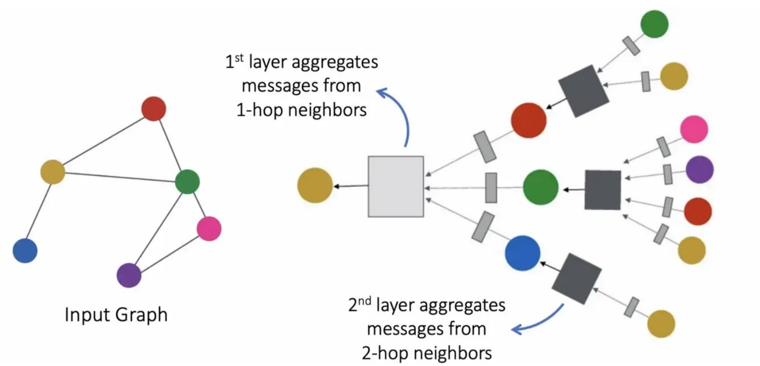


Machine Learning, in particular Deep Learning

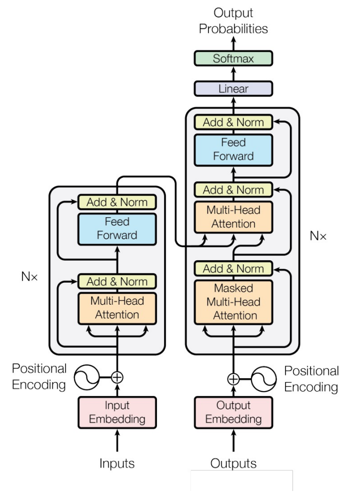
data-driven approach that learns patterns from raw data input (without necessarily understanding the underlying mechanisms of the system).



*MLP*

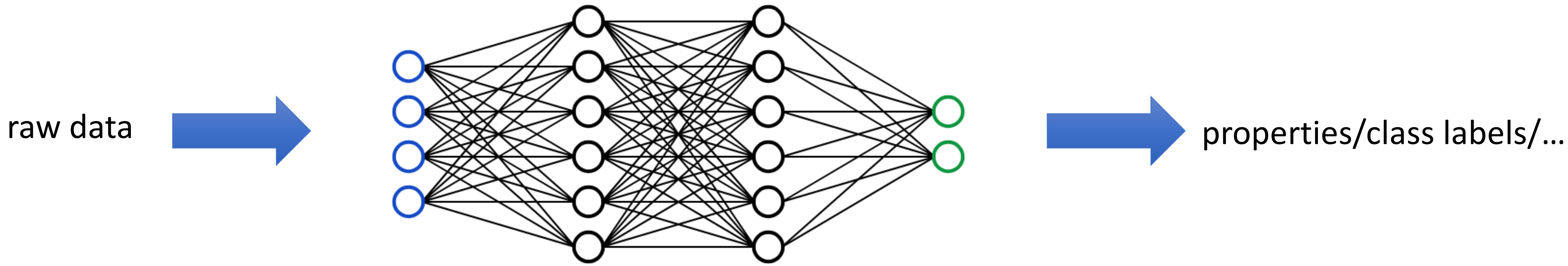



*GNN*




*Transformer*

# Machine Learning (with Neural Networks)

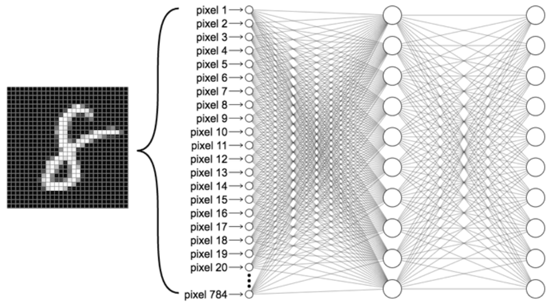


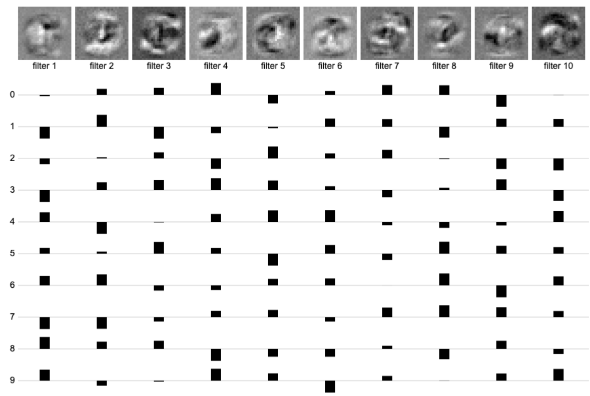

Typical setting:

- **inverse problem**: from data to properties
- train **discriminative models** with low inductive bias (e.g. large number of neurons, several layers)
- detect **statistical relationships (patterns)** between input and output

# Advantages of Deep Learning

- discriminative/inverse models: extremely **accurate** and **fast** in making **predictions** (once it is trained on a well-defined domain with many examples)
- very **flexible**: not limited by human imagination
- able to process **high-dimensional data**



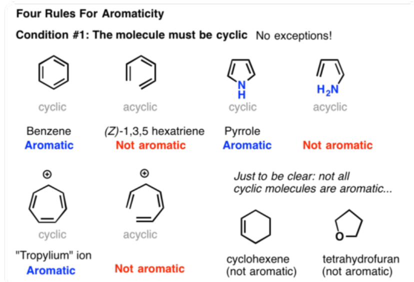



# Drawbacks of “pure” deep learning (1/2)

**Over-reliance on Data:**

- requires vast amounts of labeled data to perform accurately
- collecting and annotating is time-consuming, expensive, and often impractical

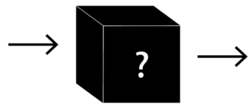
**Poor Integration of Existing Domain Knowledge:**




- no utilization of existing knowledge (focus on raw data-driven insights)
- sub-optimal or even incorrect solutions

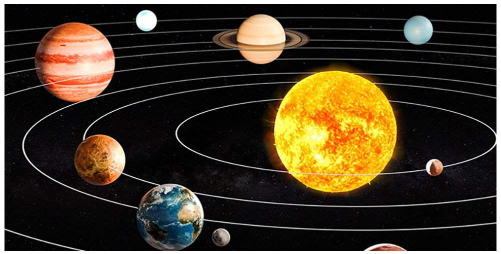
# Drawbacks of "pure" deep learning (1/2)

**Lack of Interpretability:**



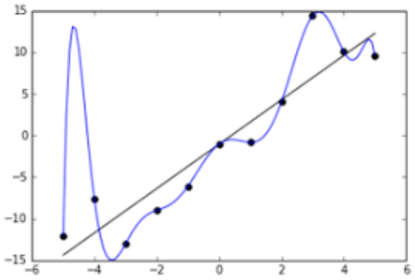

- neural networks are "black boxes"
- understanding a particular decision or prediction is difficult
- but important for sensitive applications (e.g. healthcare) and novel scientific insights

*NNs can accurately predict planetary motion. But: Can we extract the underlying mechanism of planetary motions from NNs?*



# Drawbacks of “pure” deep learning (2/2)

**Overfitting:**




- NNs with more parameters can overfit the training data
- poor generalization to new or unseen data and limited reusability

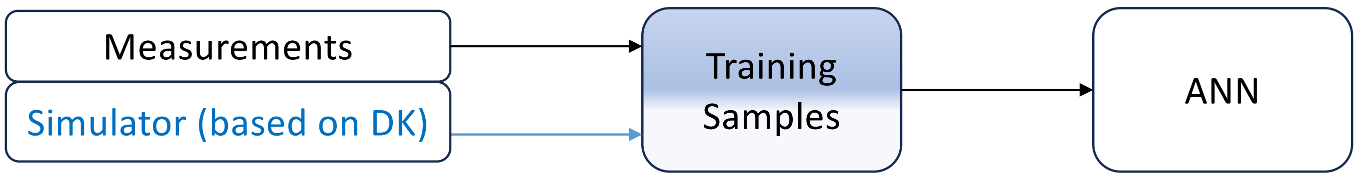
**Lack of Robustness:**

- fail unexpectedly under slight variations in input data
- but: robustness is required for critical applications where failure is not an option

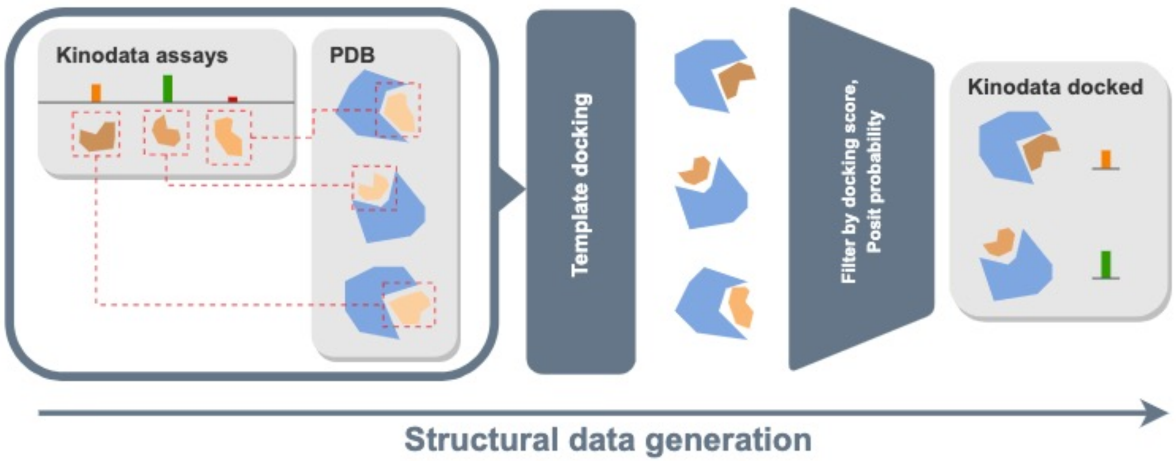
But how can we inject expert knowledge and information from mechanistic models into neural networks?

# Integrating Domain Knowledge into Neural Networks (1/3)

**1. Observational Bias:**



# Example: In-silico *data augmentation* for drug discovery



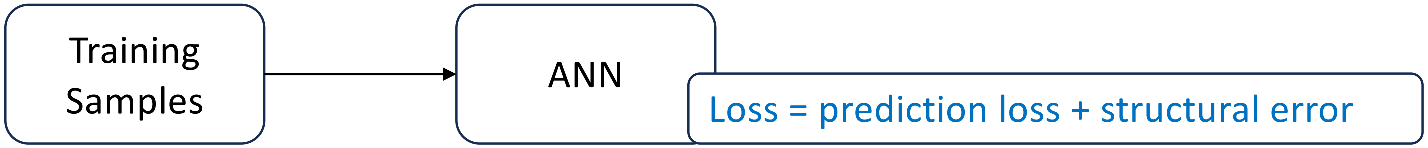

NextAID
Neuro-explicit AI for Drug Discovery

Goal: predict binding affinity for kinase ligand pairs based on 3D structures
Problem: PDB has only ~6000 samples (with 3D information)
Idea: exploit existing docking simulation methods to generate new data (3D Docking Pose & Score)
→ ~ 120 000 new samples

*Guided Docking as Data Generation Approach for Kinase-Based Deep Learning Tasks.*
*M. Backenköhler, J. Gross,* ***V. Wolf****, A. Volkamer. Submitted.*

# Integrating Domain Knowledge into Neural Networks (2/3)

**2. Learning Bias:**




e.g. Physics Informed Neural Networks

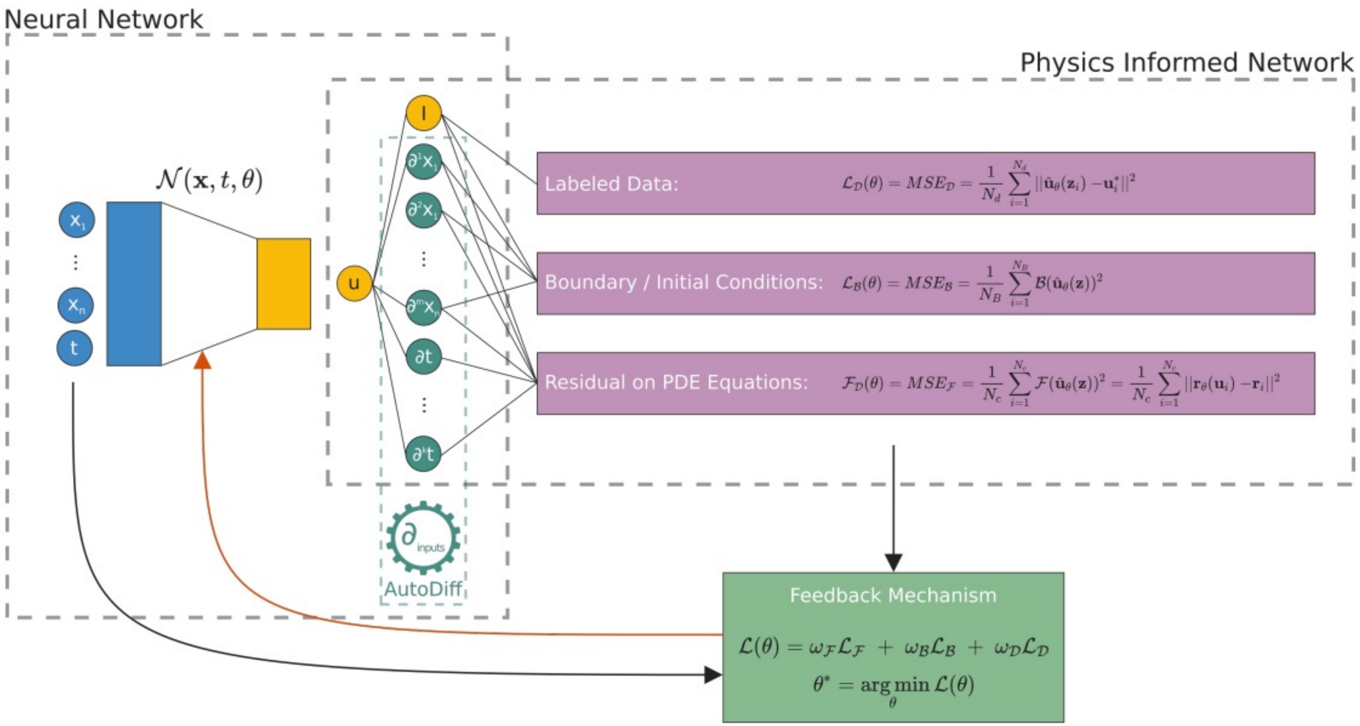



Image Source: “Scientific Machine Learning through Physics-Informed Neural Networks: Where we are and What’s next”, Cuomo et al, 2022

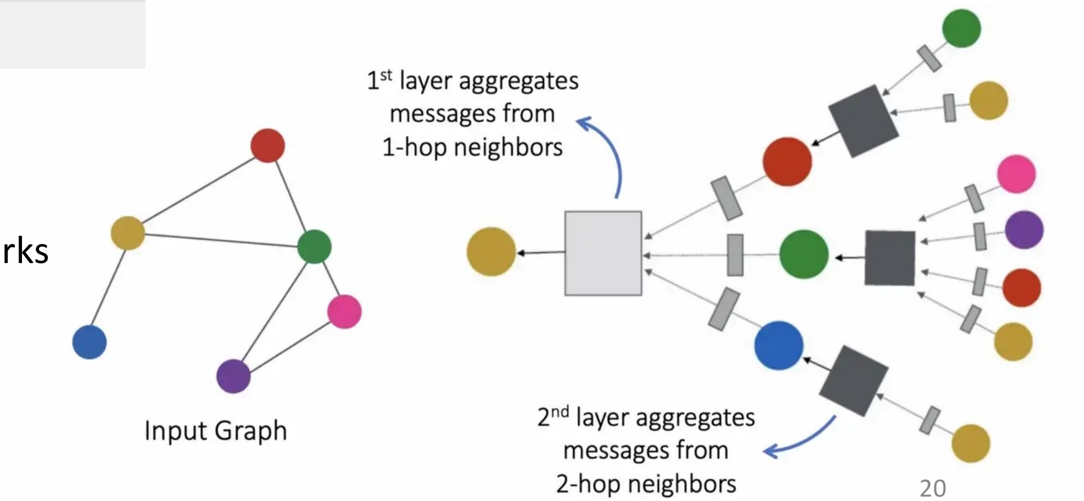
# Integrating Domain Knowledge into Neural Networks (3/3)

## **3. Inductive Bias:** e.g. relational inductive bias

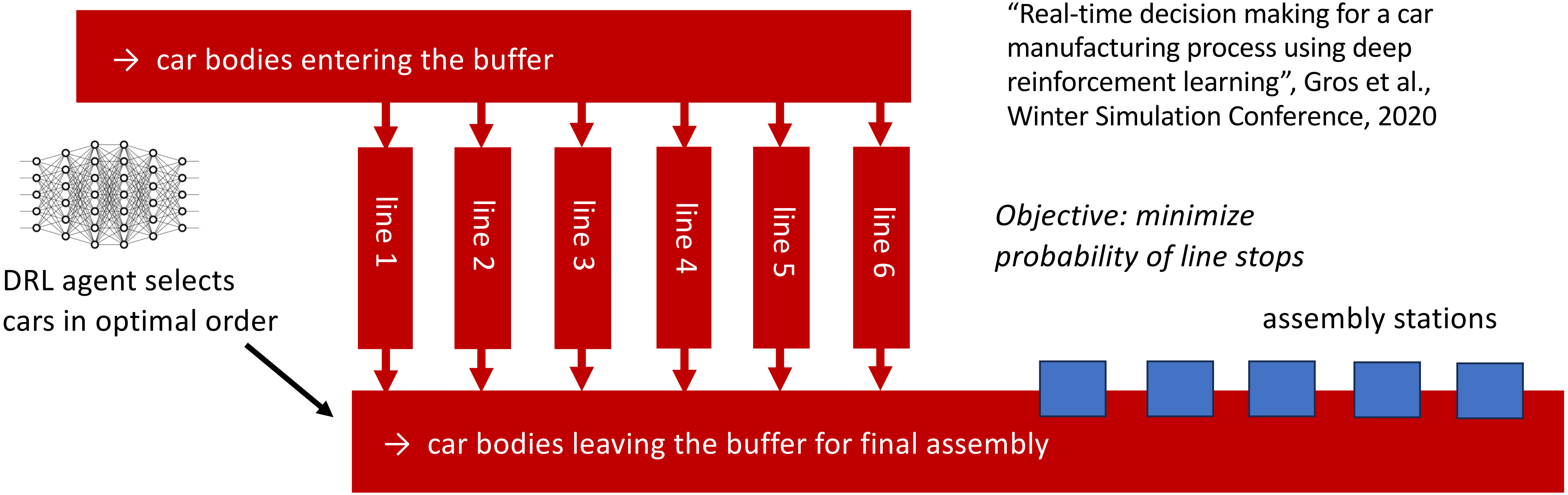
| NN Component | Entities | Relations |
|---|---|---|
| Fully connected | Units | All-to-all |
| Convolutional | Grid elements | Local |
| Recurrent | Timesteps | Sequential |
| Graph network | Nodes | Edges |

*Inductive bias allows a learning algorithm to prioritize one solution over another, independent of the observed data (Mitchell, 1980)*

Graph Neural Networks



# Example: Optimal sequence control in an automotive plant




"Real-time decision making for a car manufacturing process using deep reinforcement learning", Gros et al., Winter Simulation Conference, 2020

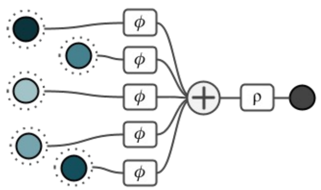
DRL agent selects cars in optimal order

*Objective: minimize probability of line stops*

Exploit known symmetries: train the NN such that solution is independent of line enumeration.

e.g. use "Deep Sets"

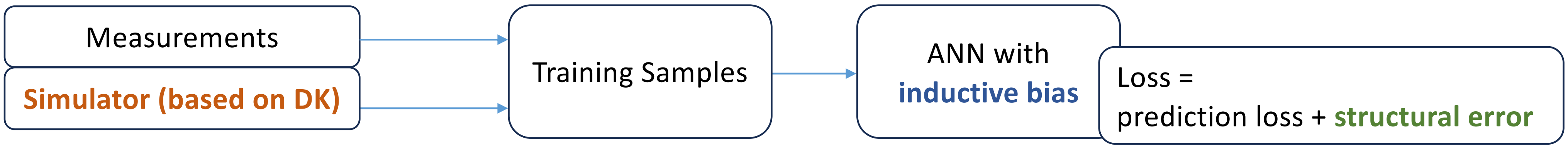
"Deep Sets", Zaheer et al, 2017



# Integrating Domain Knowledge into Neural Networks

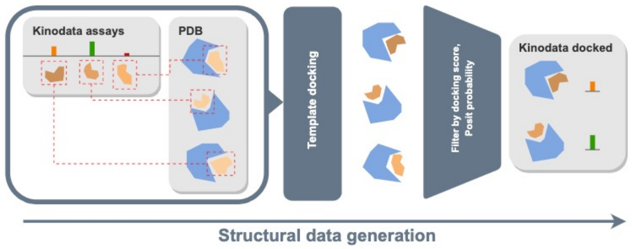
1. **Observational Bias:** data augmentation
2. **Learning Bias:** informed loss function/ constraint-based regularization terms
3. **Inductive Bias:** adapt network architecture/information flow in the NN

*Often it is a combination of these three!*



# The Promise of Hybrid AI Approaches

*Don't try to learn what you already know: guide the learning (loss; data) according to existing knowledge/mechanistic models and give inductive biases.*




→ model is more robust
→ need less training samples
→ better generalize to unseen data
→ more understandable and may drive forward scientific understanding

# Acknowledgements

## PhD Students and Post-Docs

Dr. Gerrit Grossmann

Timo Gros

Joschka Gross

## Collaborators

Prof. Andrea Volkamer,
Helmholtz Institute for Pharmaceutical Research Saarland

Prof. Luca Bortolussi,
University of Trieste

*Thank you for your attention!*

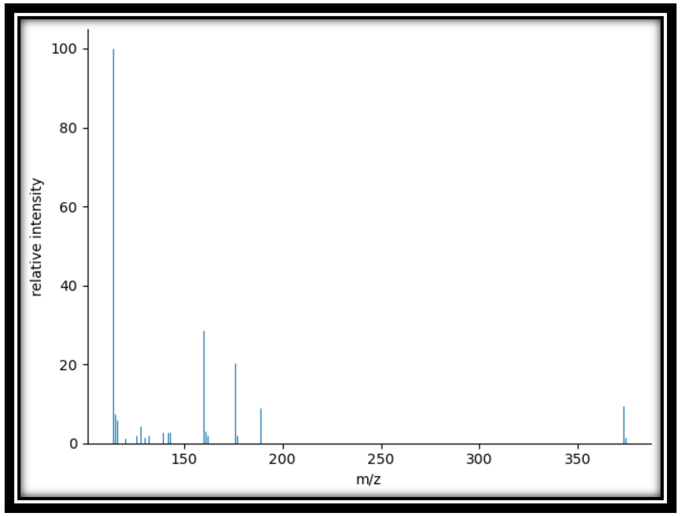
dfki ai

# Some extra slides

# Integrating Domain Knowledge into Neural Networks (2/3)

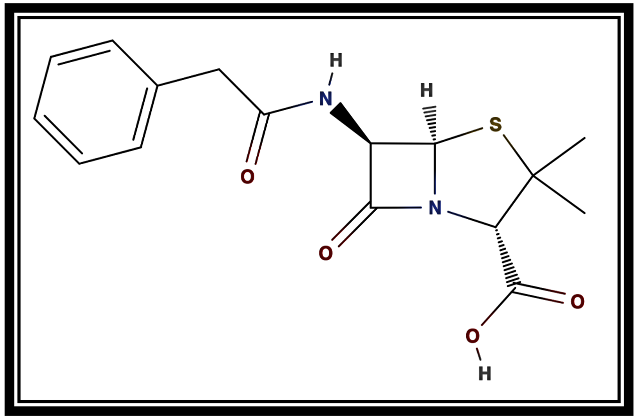
## Example: Natural Product Discovery

- Easy if compound is part of a **spectral database**
- **However: database size is microscopic** compared to natural product space!

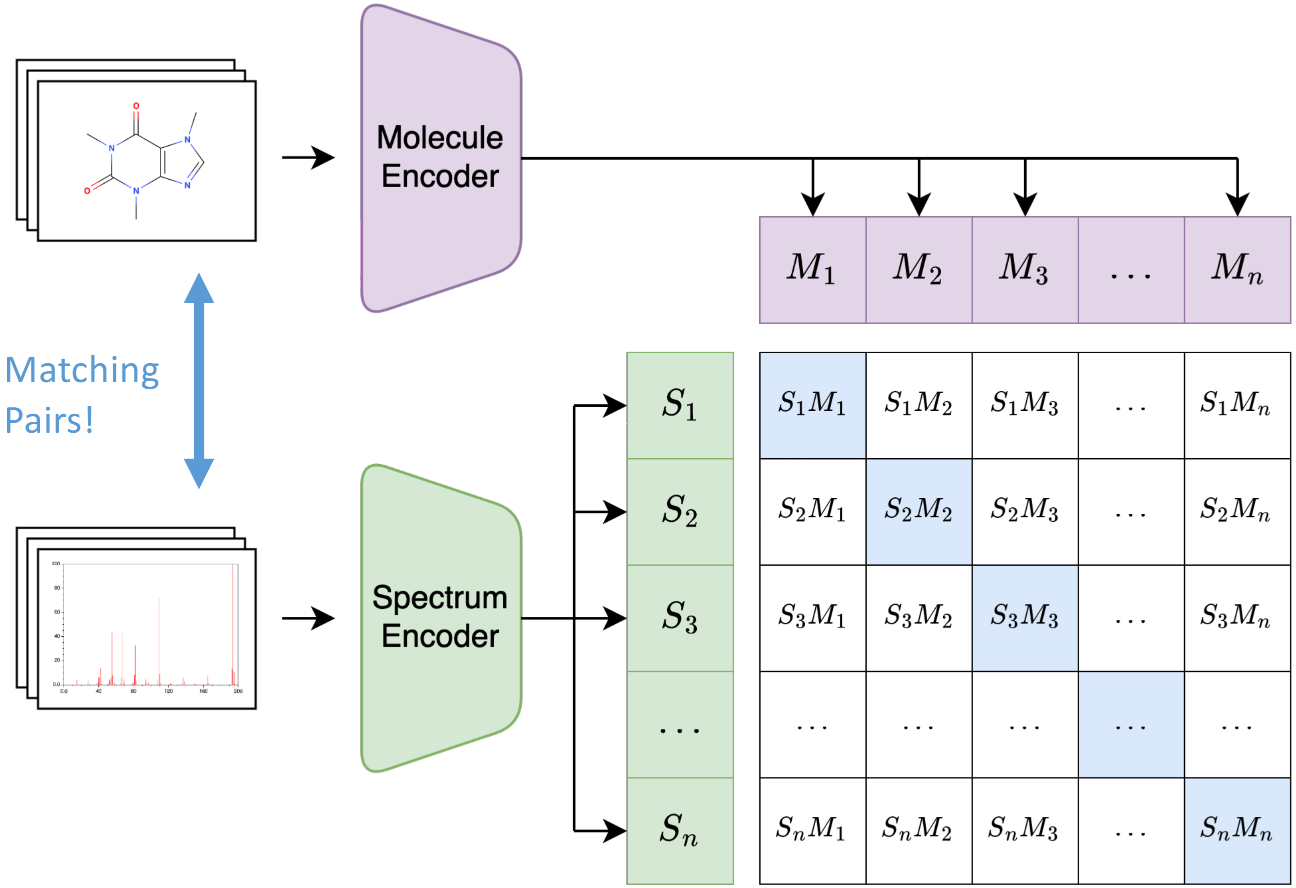



Tandem mass spectrometry (MS/MS)

Structural elucidation



# Contrastive MS/MS – metabolite latent space




- Learn a contrastive latent space
- Maximize similarity of matching molecular and spectral embeddings
- Trained on NIST23 (~600k data points, ie, matching pairs)

# GNNs