Adaptive Simulation Models

Adelinde Uhrmacher

Institute of Visual and Analytic Computing

University of Rostock

Universität Rostock

Traditio et Innovatio

Simulation model

"To an observer B, an object A* is a model of an object A to the extent that B can use A* to answer questions that interest him about A".

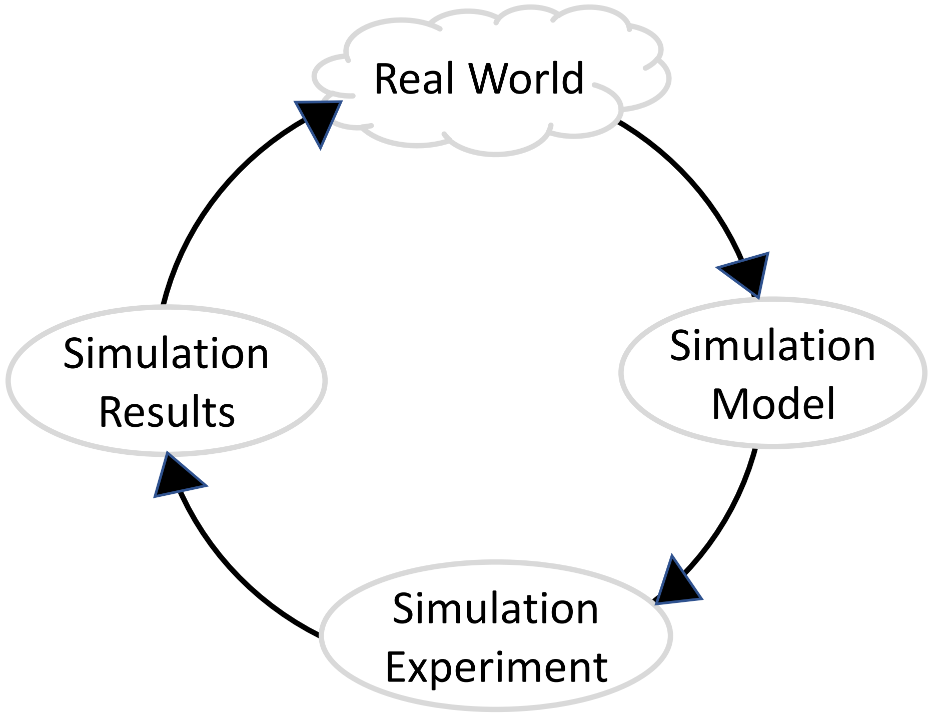
(Marvin Minsky, 1965)

Object A as a dynamic system may change significantly, e.g., via succession or regime shifts.

Observers B may change his or her questions over time.

And observers B may change .....

So simulation models must be ***adaptive*** to be relied on for predictions and insights.

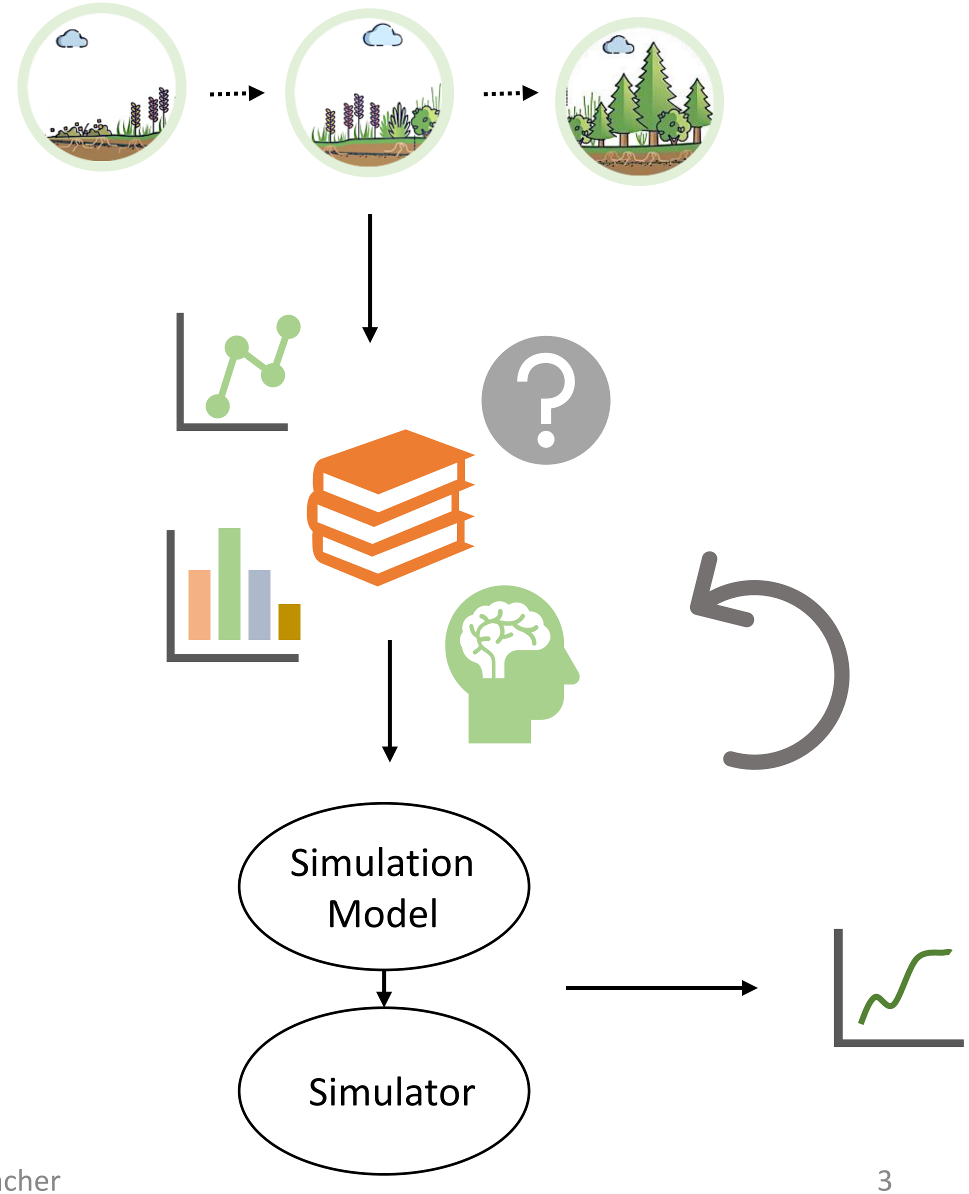


Adaptations as part of a simulation model

The system to be modeled exhibit structural change, e.g., succession.

Building simulation models usually involves knowledge (hypotheses about mechanisms), data (e.g., kinetic parameters, time series).

Intricate processes of model building, refinement, analysis, calibration, and validation.



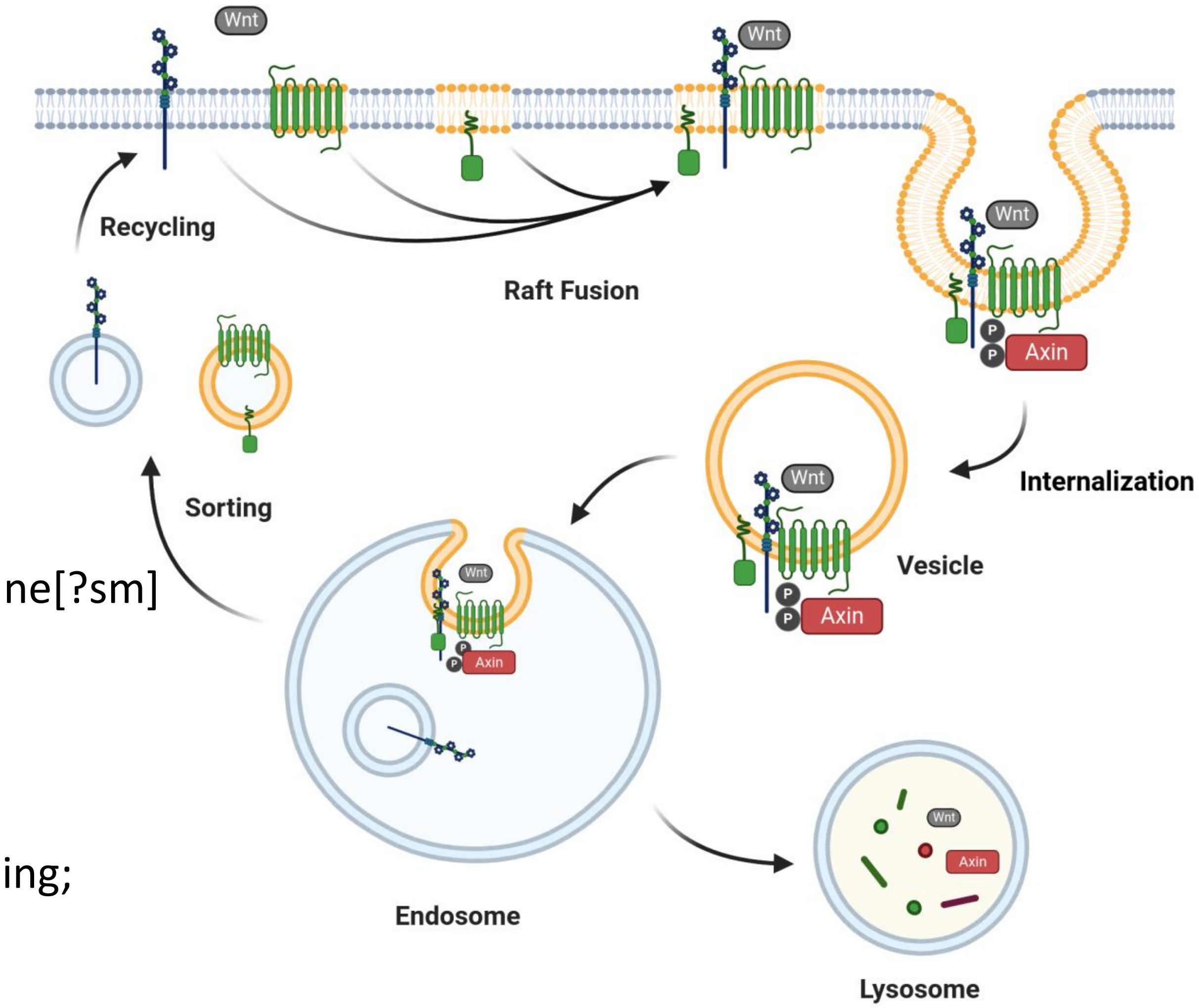
Endocytosis

// Raft Fusion
Cell[Membrane[Raft:r1[?sr1] + Raft:r2[?sr2]]] ->
Cell[Membrane[Raft:r1[?sr1 + ?sr2]]] @ kRaftFusion;

// Raft internalization
Cell[Membrane[Raft[?sr] + ?sm] + ?sc] -> Cell[Membrane[?sm]
+ Endosome[Raft[?sr]] + ?sc] @ kEndo;

// Recycling
Cell[Endosome[?se] + Membrane[?sm] + ?sc] ->
Cell[Membrane[?se + ?sm] + ?sc] @ kEndosomeRecycling;

// Degradation
Cell[Endosome + ?sc] -> Cell[?sc]



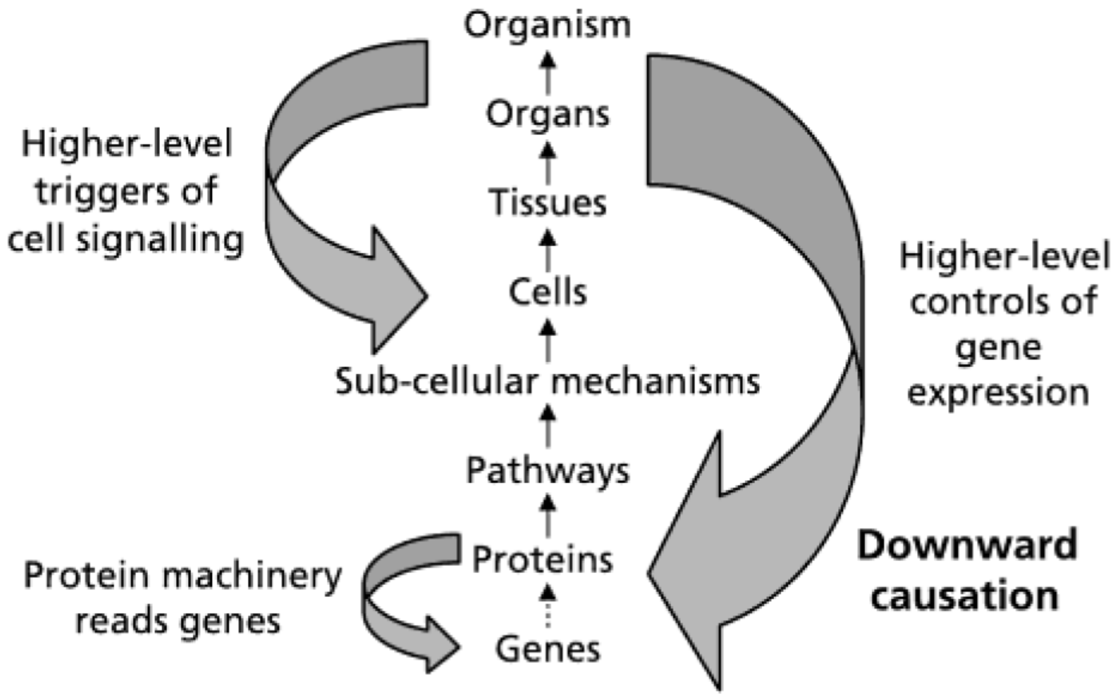
Haack F., Budde K. and Uhrmacher, A. M. (2020) Exploring mechanistic and temporal regulation of LRP6 endocytosis in canonical WNT signaling. Journal of Cell Science, 133 (15).

Sufficiently expressive domain-specific modeling language (and efficient simulator)

How to describe it: the syntax of the domain-specific modeling language should reflect the metaphors of the domain, e.g., biochemical reactions.

What to describe: the semantics of the domain-specific modeling language should reflect the requirements of the domain, e.g., Continuous Time Markov Chain semantics.

In addition, important characteristics need to be reflected, e.g., multi-level (up- and downward causations) or **dynamic structures**.



Denis Noble (2006). The Music of Life. Oxford University Press.

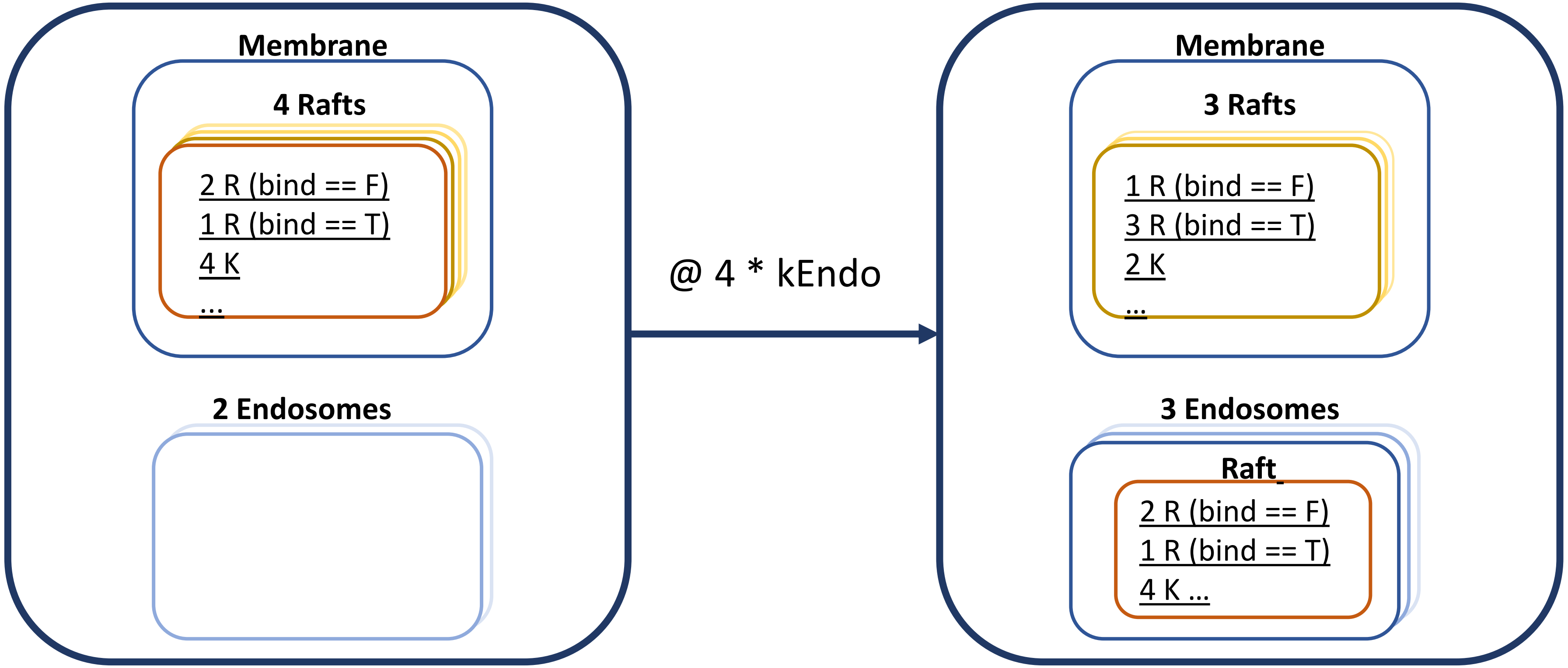
ML-Rules

// Raft internalization

Cell[Membrane[Raft[?sr] + ?sm] + ?sc] ->
Cell[Membrane[?sm] + Endosome[Raft[?sr]] + ?sc] @ kEndo;

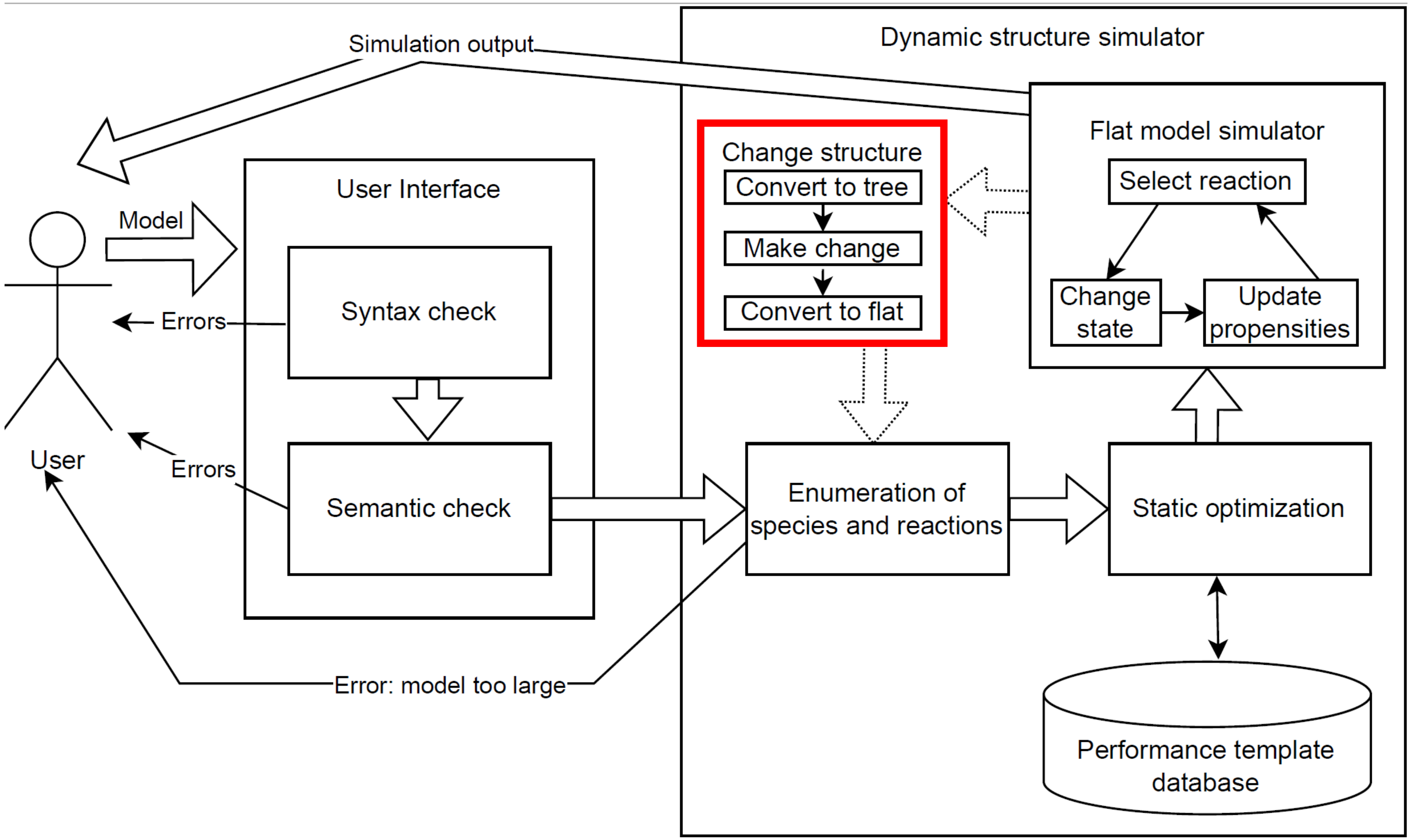
Syntax

Semantics



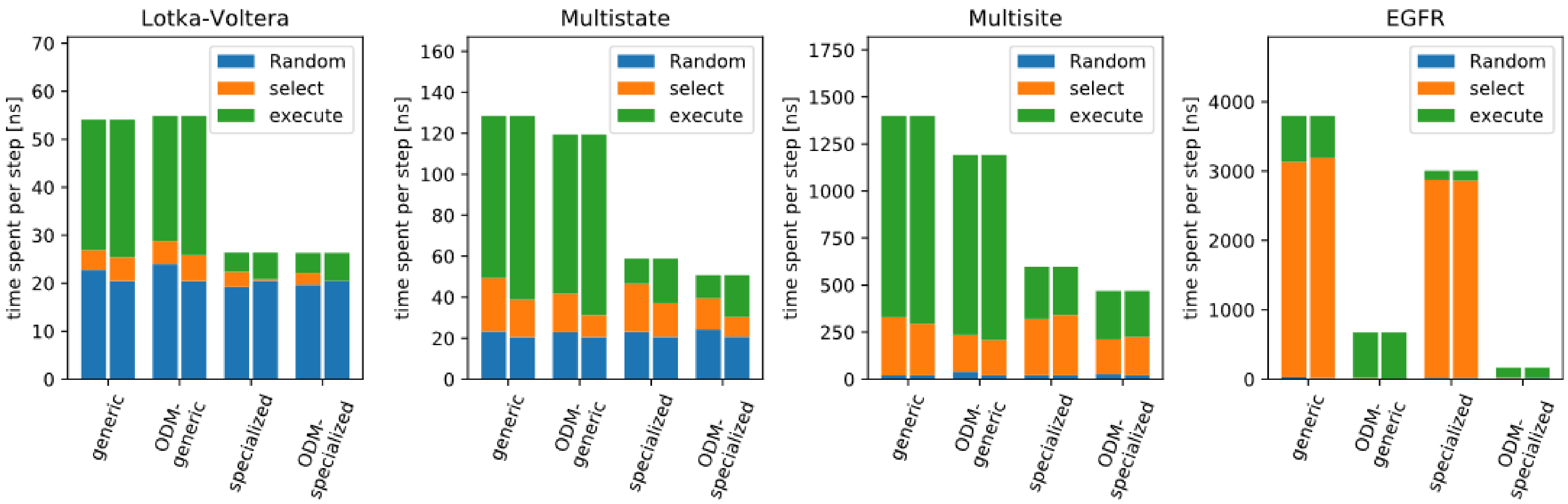
Helms T., Warnke T., Maus C., and Uhrmacher A.M. (2017): Semantics and Efficient Simulation Algorithms of an Expressive Multi-Level Modeling Language. ACM Transactions on Modeling and Computer Simulation (TOMACS), 27 (2), 8:1-8:25. ISSN 1049-3301

ML-Rules simulator with built-in adaptation



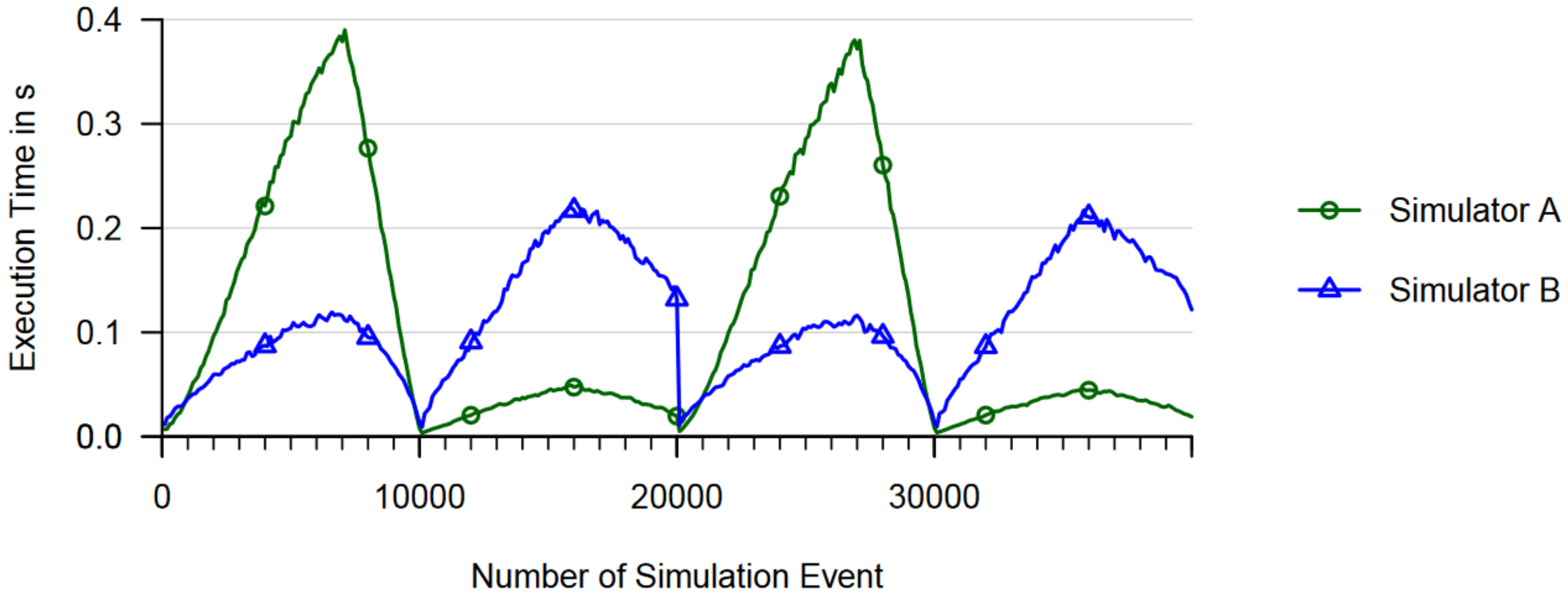
Köster Till, Henning Philipp, Warnke Tom, Uhrmacher Adelinde: Expressive modeling and fast simulation for dynamic compartments. PLOS ONE. 2024

Different models, different performance



Köster, T., Warnke, T., & Uhrmacher, A. M. (2022). Generating fast specialized simulators for stochastic reaction networks via partial evaluation. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, *32*(2), 1-25.

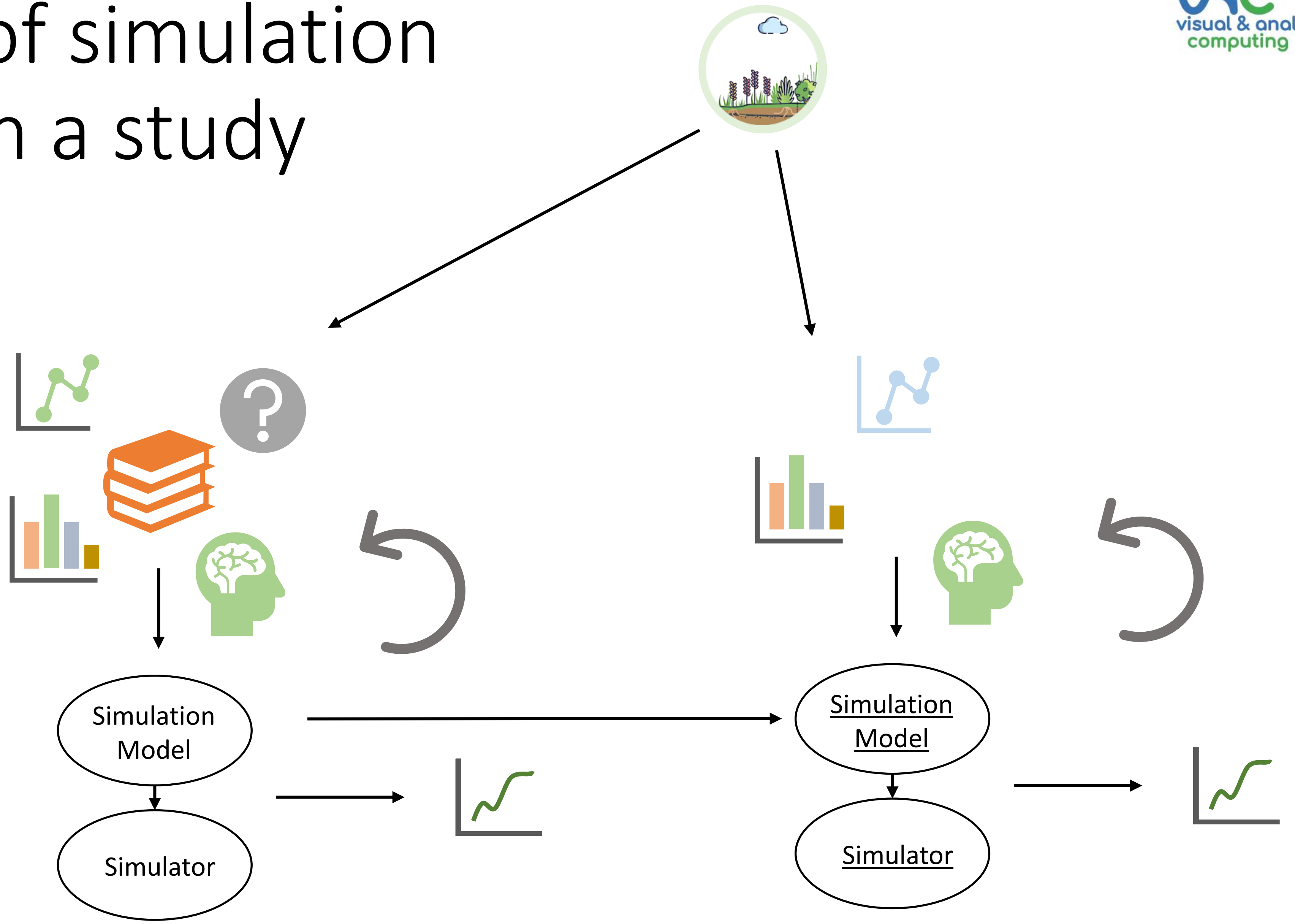
Q-learning for selecting suitable simulators

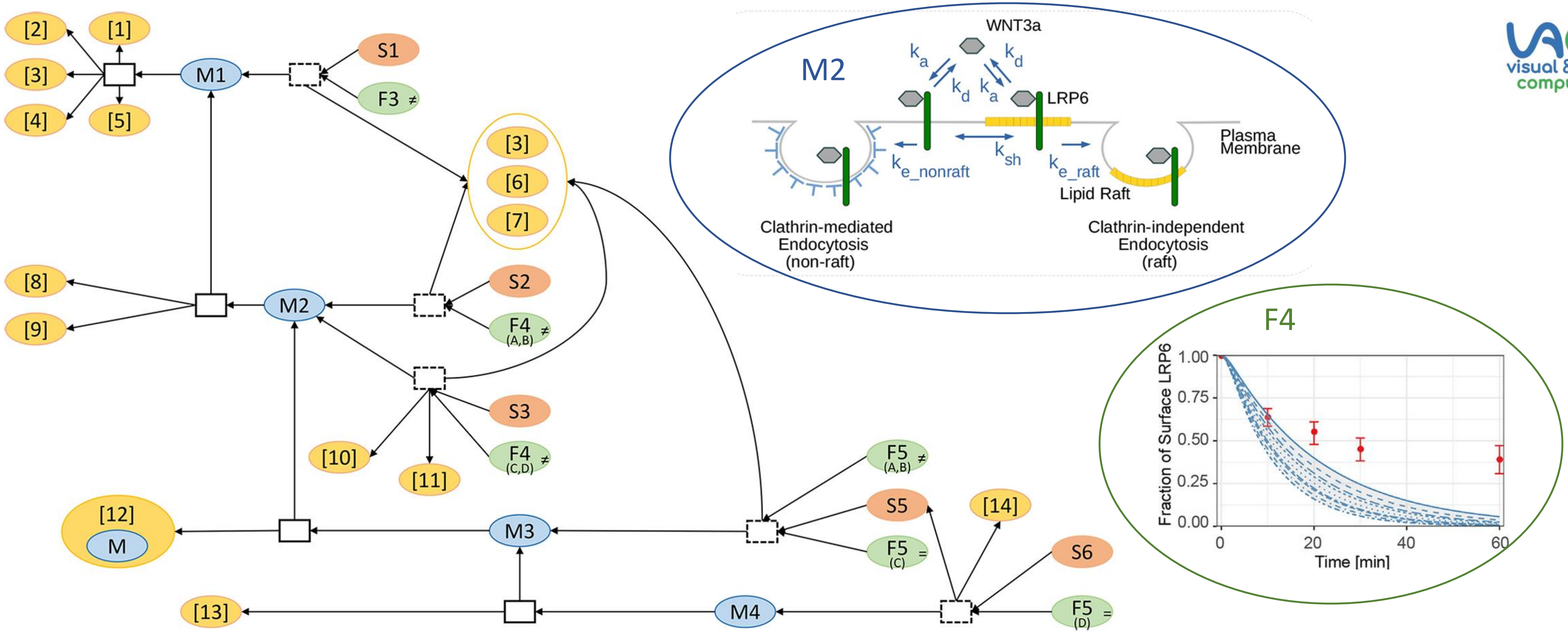


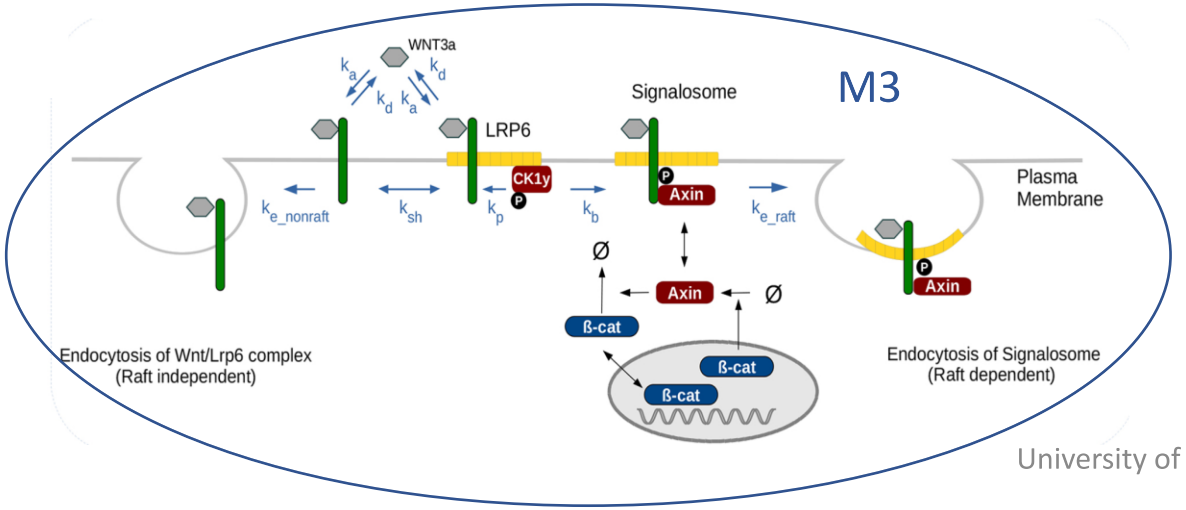
Performance of simulation algorithms varies with model properties that may change during running the simulation.

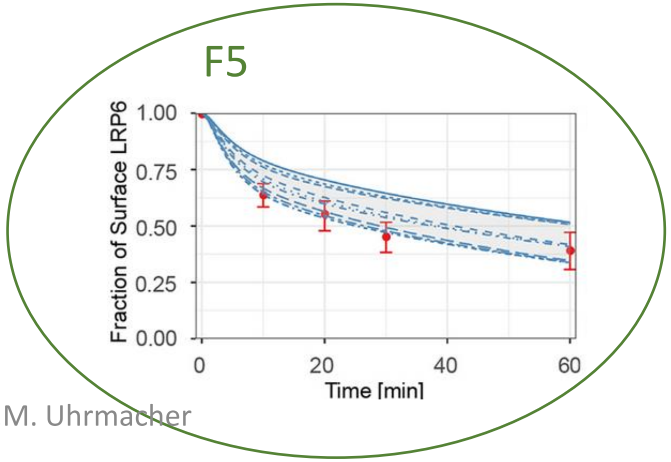
Helms, T., Ewald, R., Rybacki, S., & Uhrmacher, A. M. (2015). Automatic runtime adaptation for component-based simulation algorithms. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, *26*(1), 1-24.

Adaptation of simulation model within a study





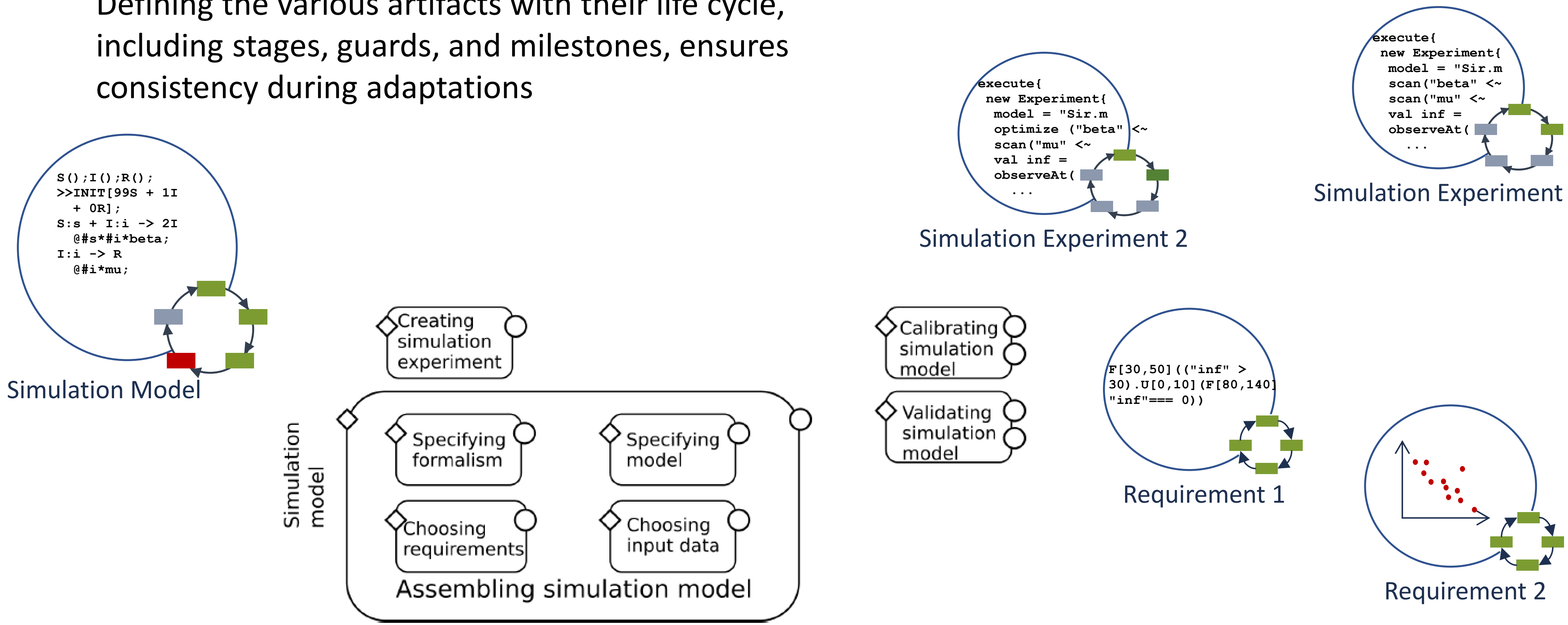




Haack, F., Budde, K., & Uhrmacher, A. M. (2020). Exploring the mechanistic and temporal regulation of LRP6 endocytosis in canonical WNT signaling. *Journal of cell science*, *133*(15), jcs243675.

An artifact-based workflow

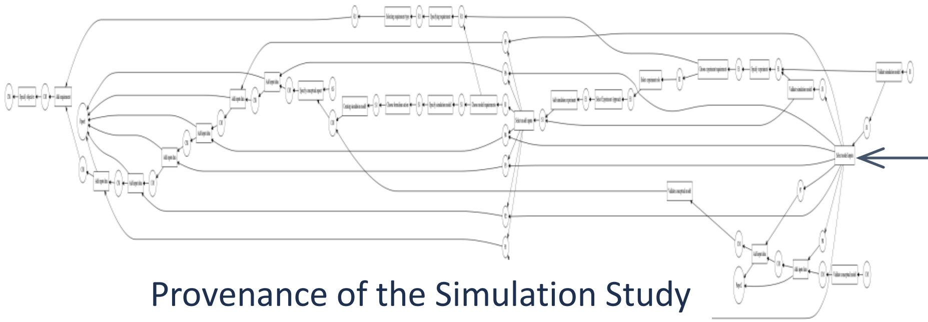
Defining the various artifacts with their life cycle, including stages, guards, and milestones, ensures consistency during adaptations



Ruscheinski, Andreas, Tom Warnke, and Adelinde M. Uhrmacher. "Artifact-based workflows for supporting simulation studies." *IEEE Transactions on Knowledge and Data Engineering* 32.6 (2019): 1064-1078.

For guiding and documentation

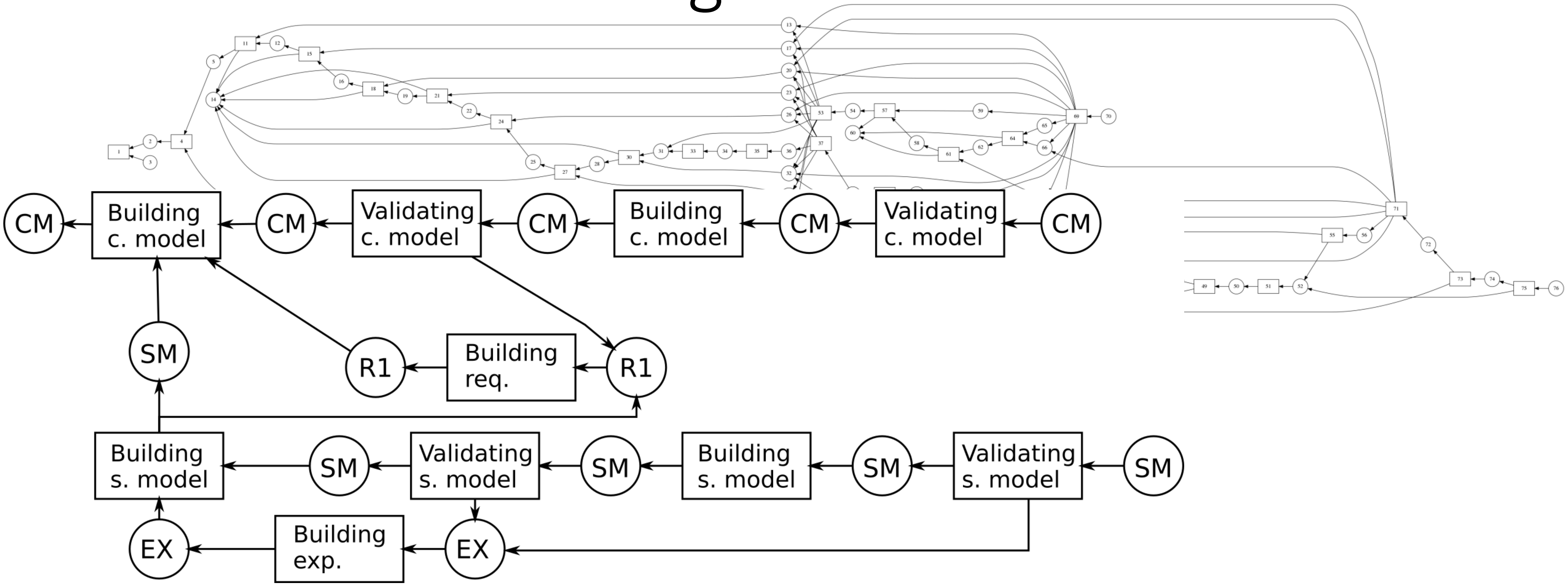
```
rule "Stage open: Validating simulation model"

when
  $sm: SimulationModel(simulationModelAssembled == true
  forall ($exp : Experiment(experimentAssembled == true) from $sm.getValidationExperiments())
     eval($sm.getRequirements().size() != 0 && $sm.getRequirements().containsAll($sm.getApprovedRequirements()))
then
  controller.getView().getEditorTabs(). …. getValidatingSimulationModelStage().activate());
```



Provenance of the Simulation Study

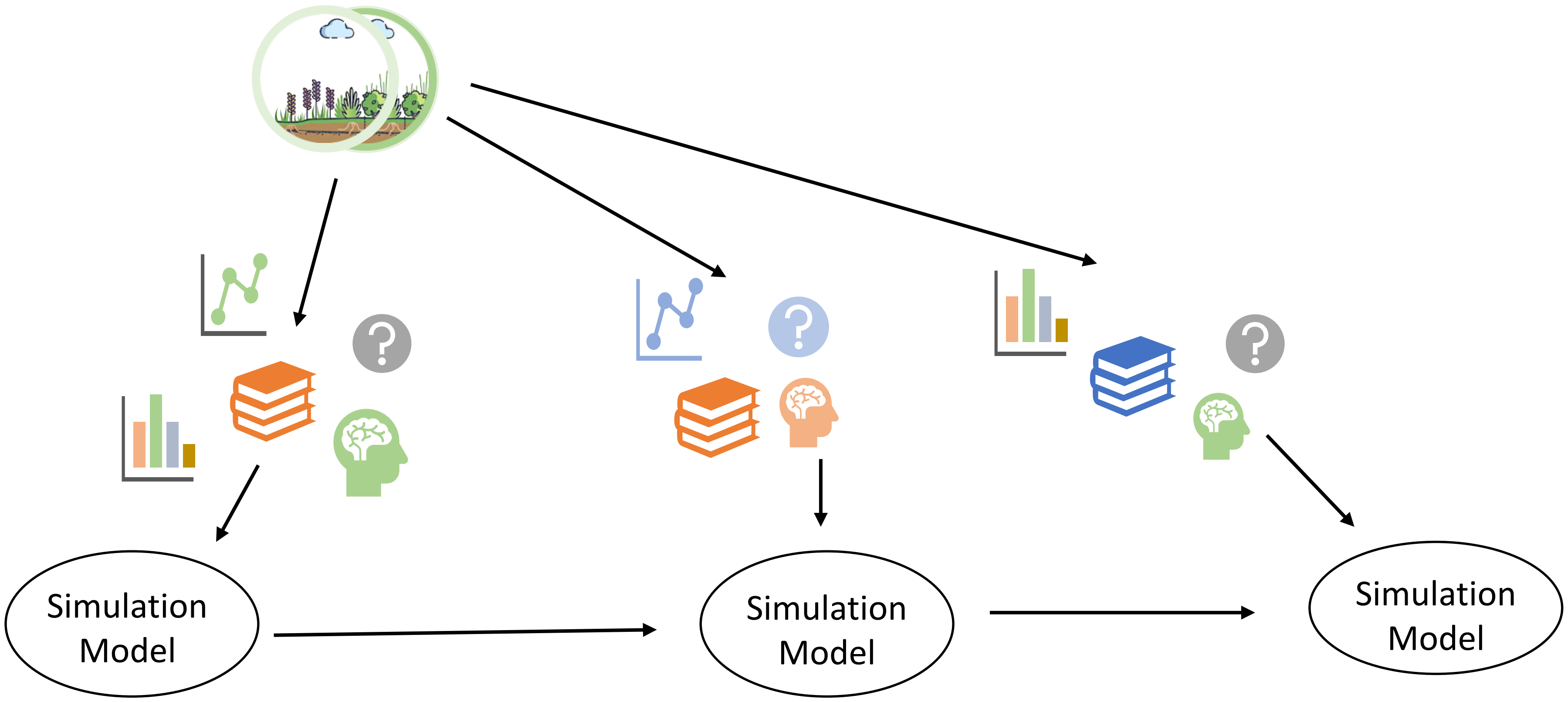
Planning the Steps ahead

Provenance – Filtering

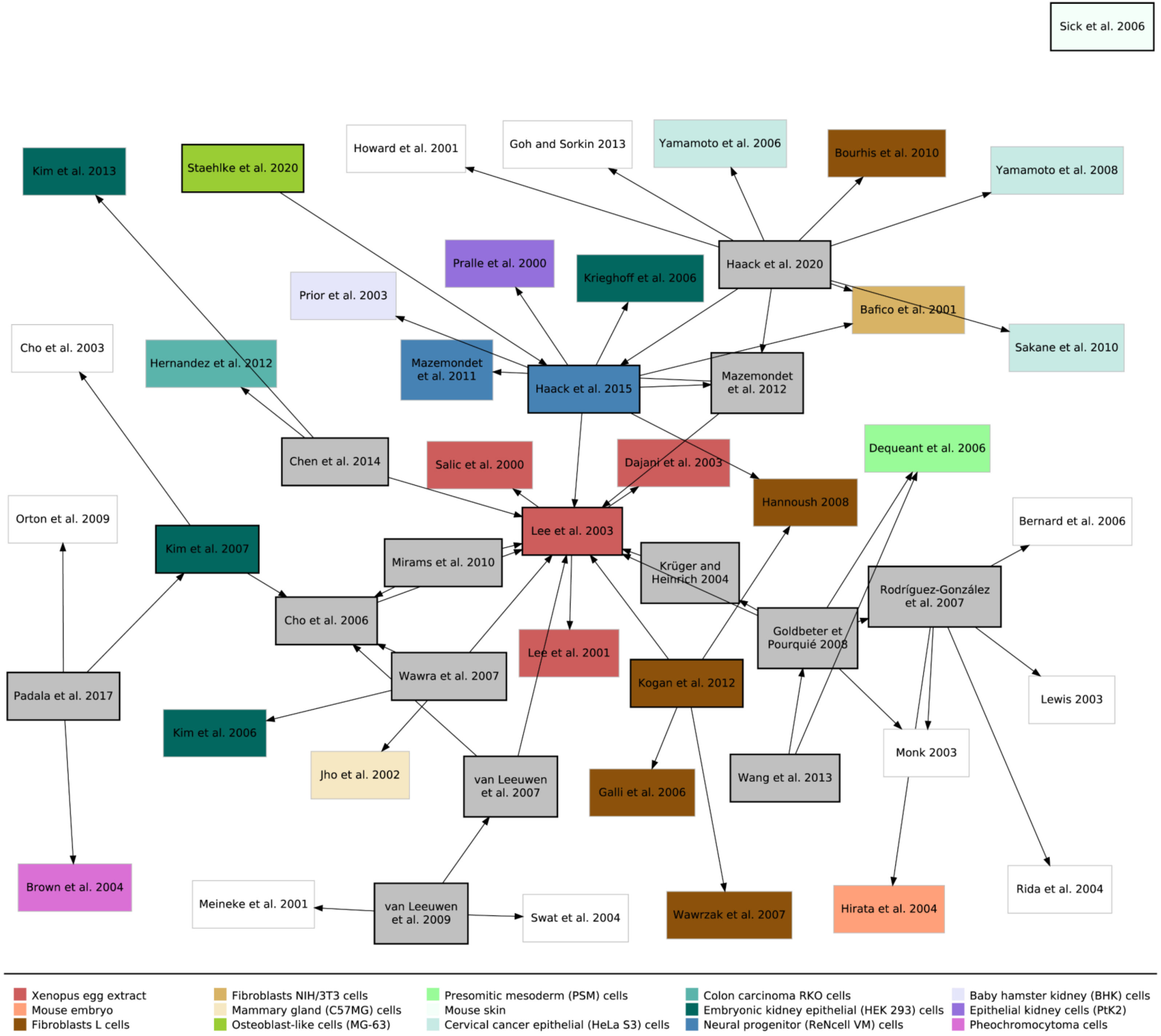


Ruscheinski, Andreas, et al. "Capturing and reporting provenance information of simulation studies based on an artifact-based workflow approach." *Proceedings of the 2019 ACM SIGSIM conference on principles of advanced discrete simulation*. 2019.

Adaptation of simulation model between studies

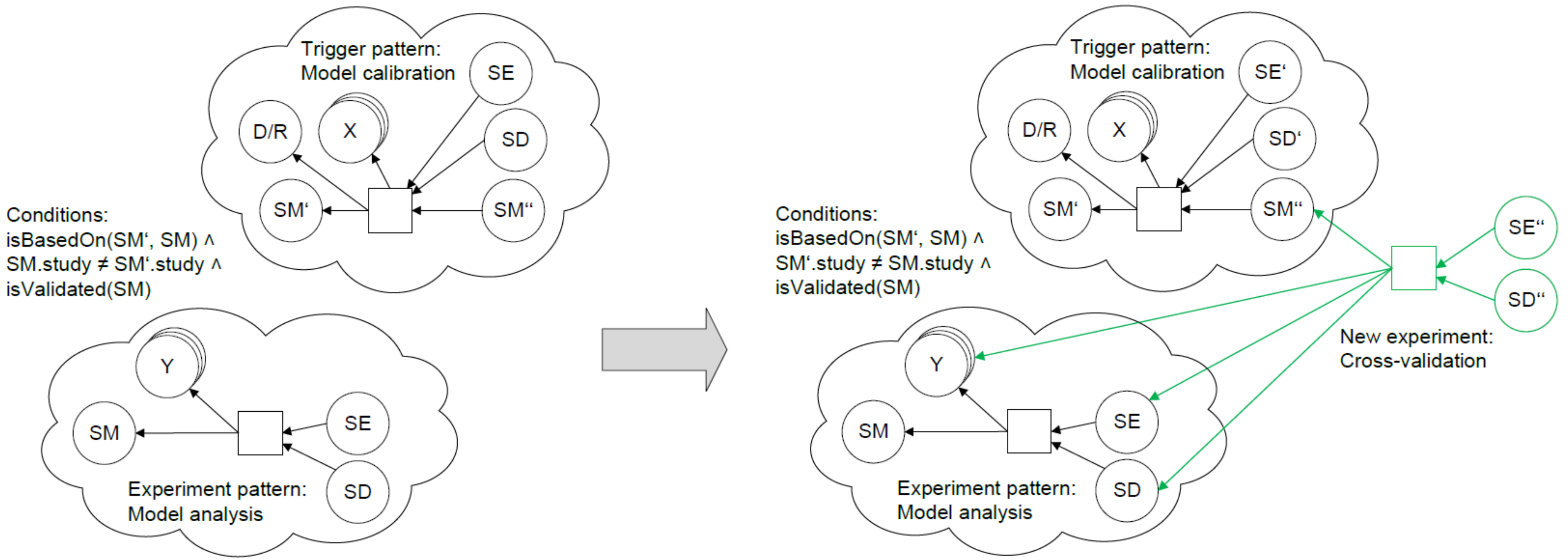


A family of WNT models



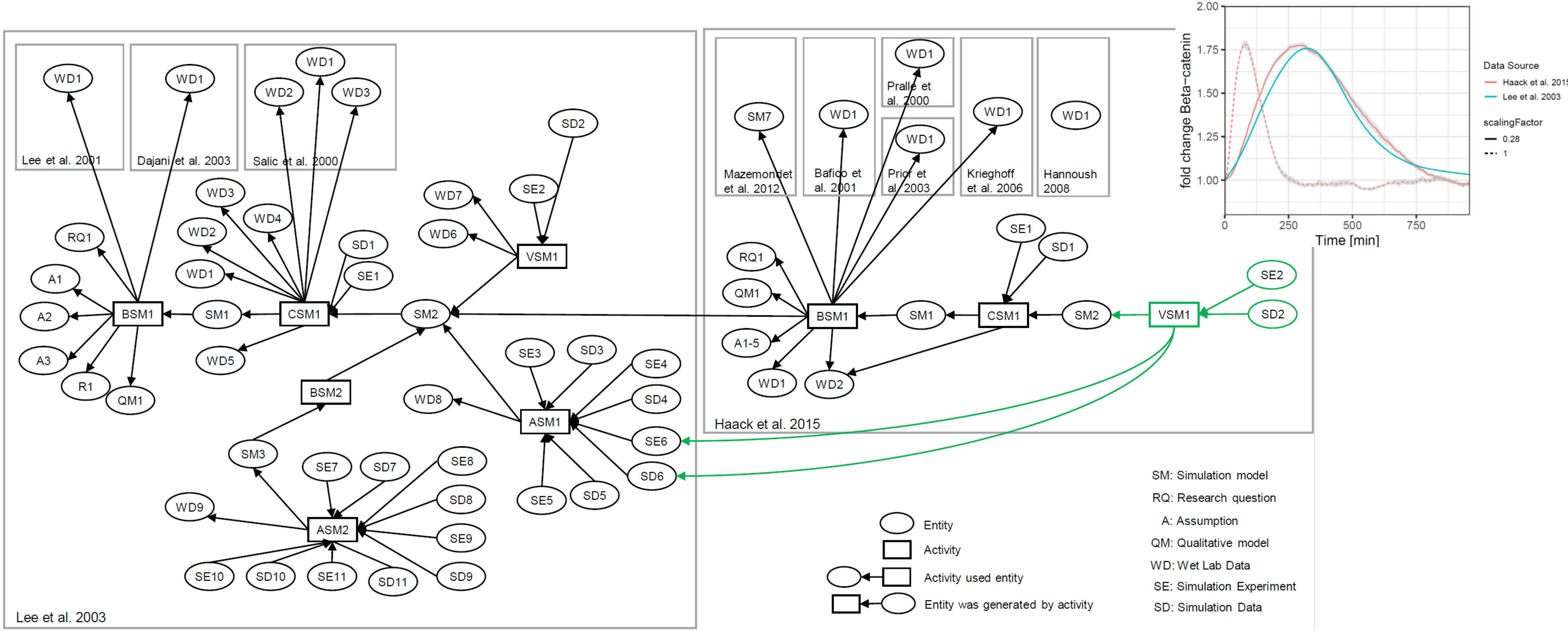
Budde, Kai, et al. "Relating simulation studies by provenance—Developing a family of Wnt signaling models." *PLOS Computational Biology* 17.8 (2021): e1009227.

Automatic generation and execution of simulation experiments



Wilsdorf, P., Wolpers, A., Hilton, J., Haack, F., & Uhrmacher, A. (2023). Automatic reuse, adaption, and execution of simulation experiments via provenance patterns. *ACM Transactions on Modeling and Computer Simulation*, *33*(1-2), 1-27.

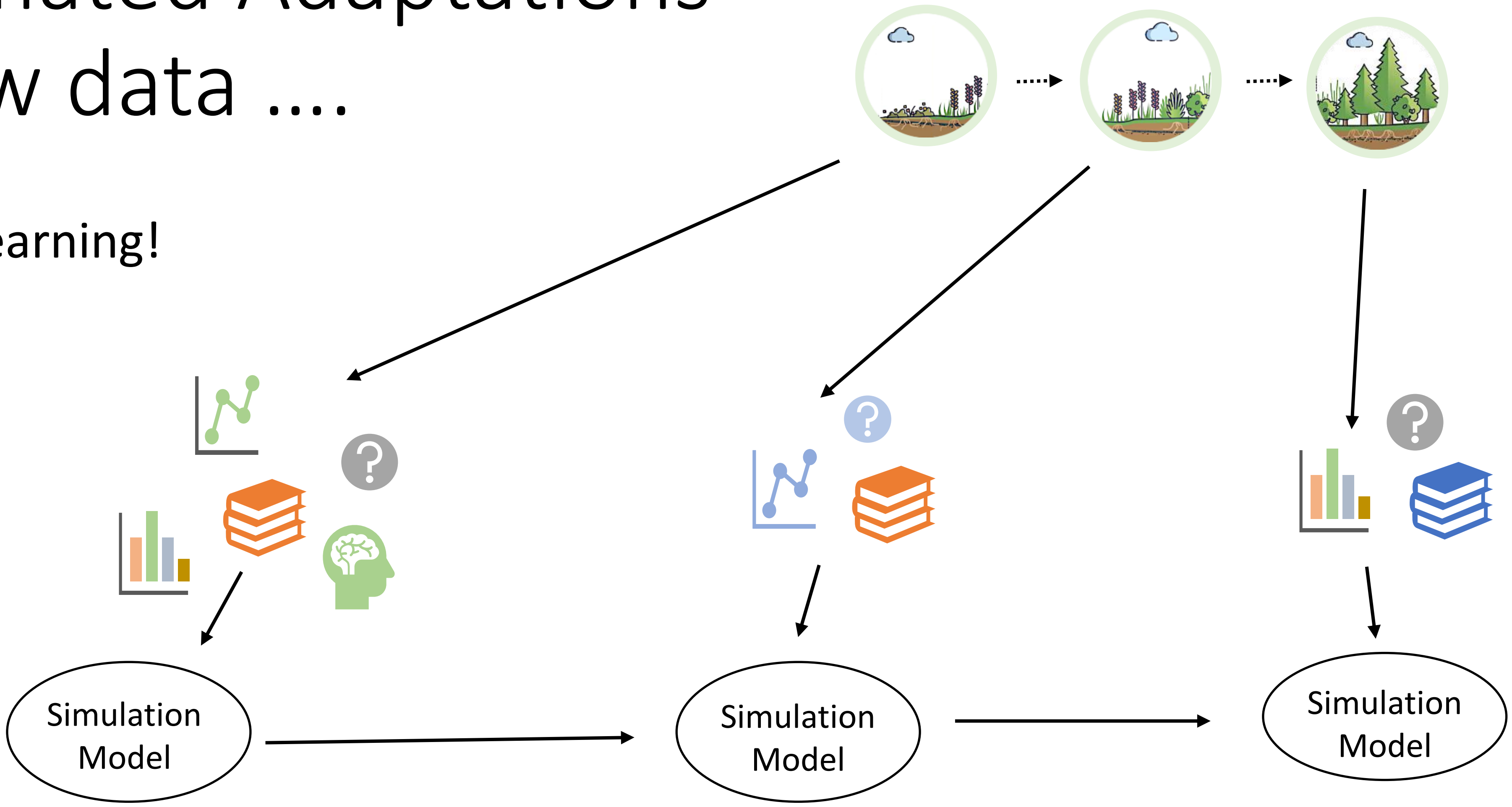
Automatic Adaption to different cell types



Wilsdorf, P., Wolpers, A., Hilton, J., Haack, F., & Uhrmacher, A. (2023). Automatic reuse, adaption, and execution of simulation experiments via provenance patterns. *ACM Transactions on Modeling and Computer Simulation*, *33*(1-2), 1-27.

Automated Adaptations to new data ….

Requires learning!

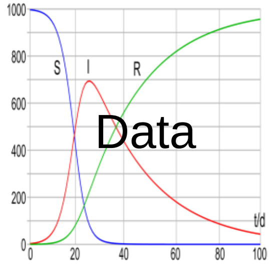


Learning models

A + B → C

Model

Simulator



Parameter estimation

R0: $S + I \xrightarrow{?} 2\,I$

R1: $I \xrightarrow{?} R$

Learning of structure + parameters

R0: $? + ? \xrightarrow{?} ?$

R1: $? \xrightarrow{?} ?$

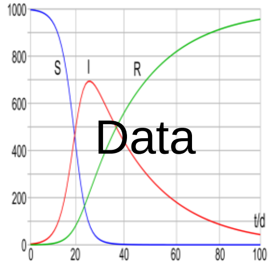
.. : $? \xrightarrow{?} ? + ?$

???

A + B → C

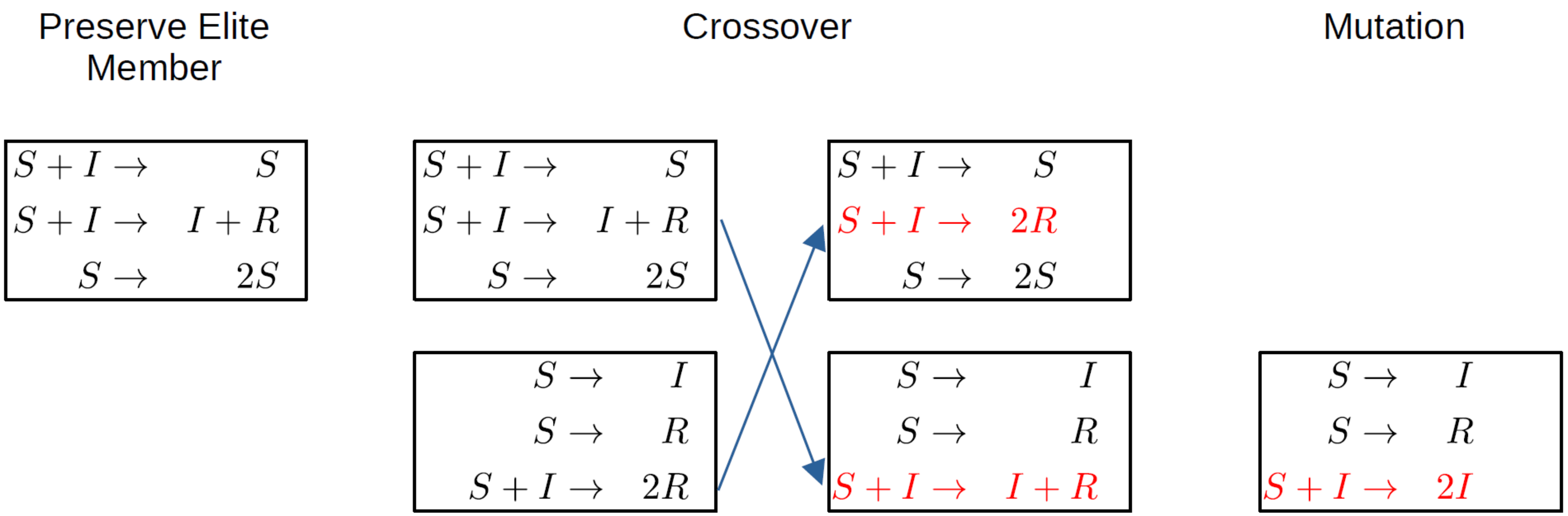
Model

Gradient of simulator,
SINDy,
GA over simulations
GA over model libraries



Kreikemeyer, J. N. and Andelfinger, P. and Uhrmacher A. M. (2024). Towards Learning Stochastic Population Models by Gradient Descent. Proceedings of SIGSIM Principles of Advanced Discrete Simulation (PADS ’24)

Evolving libraries



Kreikemeyer, Justin N. and Burrage, Kevin and Uhrmacher, Adelinde M. (2024) *Discovering Biochemical Reaction Models by Evolving Libraries.* In: 22nd International conference on Computational Methods in System Biology (CMSB 2024), 16-18 Sep 2024, Pisa, Italy. Proceedings, published by Springer Nature Switzerland, Cham, pp. 117-136.

For a simple SIR model ...

$$\begin{aligned} S + I &\xrightarrow{0.02} 2I \\ I &\xrightarrow{5} R \end{aligned}$$

ground truth

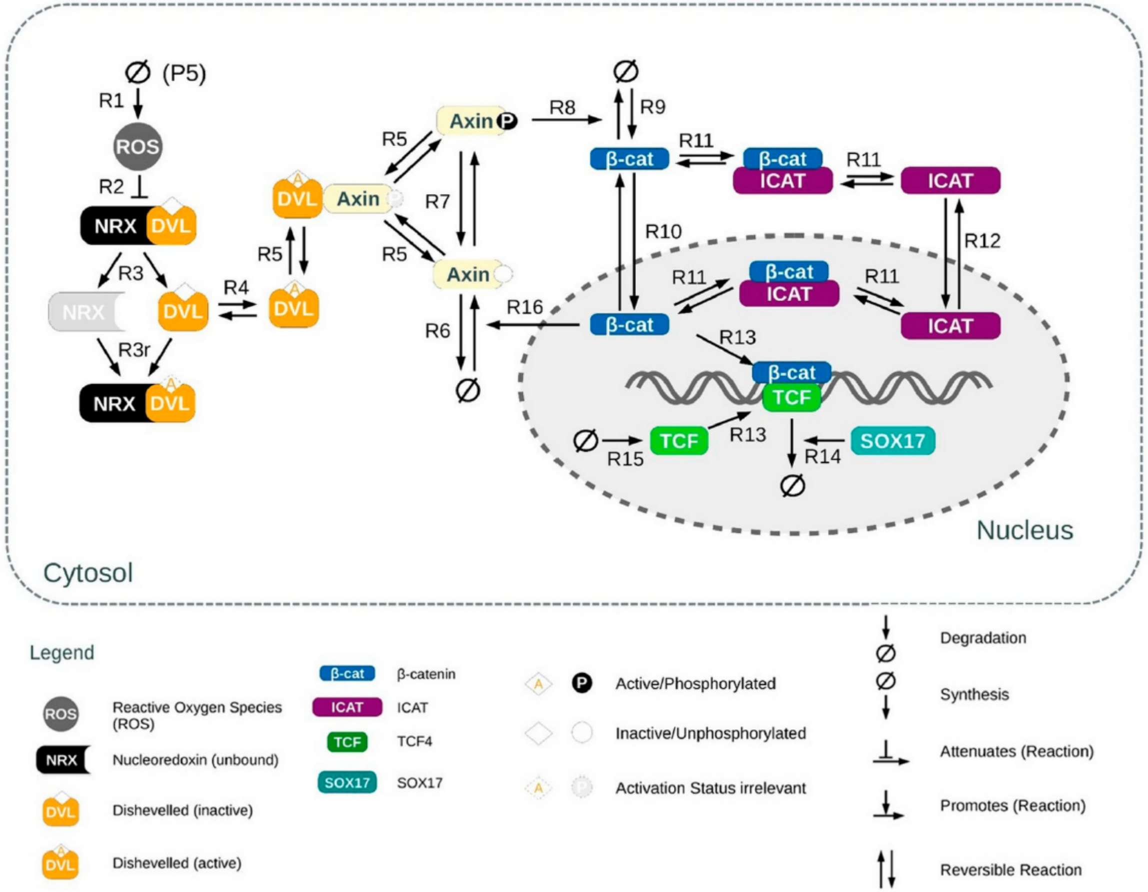
$$\begin{aligned}
S + R &\xrightarrow{0.00021} 2S + I \\
S + I &\xrightarrow{0.017} 2I \\
2I &\xrightarrow{3e-05} 3I \\
2I &\xrightarrow{0.0051} I + R \\
I + R &\xrightarrow{2.9e-06} S + I + R \\
I + R &\xrightarrow{0.0025} 2R \\
S + R &\xrightarrow{0.00041} I + 2R \\
S + I &\xrightarrow{0.0013} R \\
S + I &\xrightarrow{0.0013} 2I + R \\
I + R &\xrightarrow{8.5e-06} S \\
S + R &\xrightarrow{0.00088} I \\
2S &\xrightarrow{3.6e-05} S + I \\
2S &\xrightarrow{1.2e-06} S
\end{aligned}$$

coupled SINDy

$$\begin{aligned} S + I &\xrightarrow{0.02} 2I \\ I &\xrightarrow{5} R \end{aligned}$$

evolving libraries
+ coupled SINDy

Can realistic models be learned? – Back to Wnt



flatten

$$
\begin{array}{rcl}
 & \xrightarrow{6e+02} & Bcata \\
NucBcata & \xrightarrow{0.14} & Bcata \\
Axinp + Bcati & \xrightarrow{0.00021} & Axinp \\
Bcati & \xrightarrow{0.00011} & \\
NucICAT + NucBcata & \xrightarrow{0.1} & NucBcati \\
Axinu & \xrightarrow{0.03} & Axinp \\
NrxnO + Rosa & \xrightarrow{5e+02} & NrxO \\
NrxO & \xrightarrow{0.02} & NrxnO \\
Dvli & \xrightarrow{0.0005} & Dvla \\
DvlAxinu & \xrightarrow{0.068} & Dvla + Axinu \\
Counter & \xrightarrow{0.2} & Counter + Rosa \\
 & \xrightarrow{1} & Counter \\
\ldots & &
\end{array}
$$

[4] S. Staehlke et al. 2020. ROS Dependent Wnt/β-Catenin Pathway and Its Regulation on Defined Micro-Pillars—A Combined In Vitro and In Silico Study. Cells 2020 9, 1784. https://doi.org/10.3390/cells9081784

Yes, but …

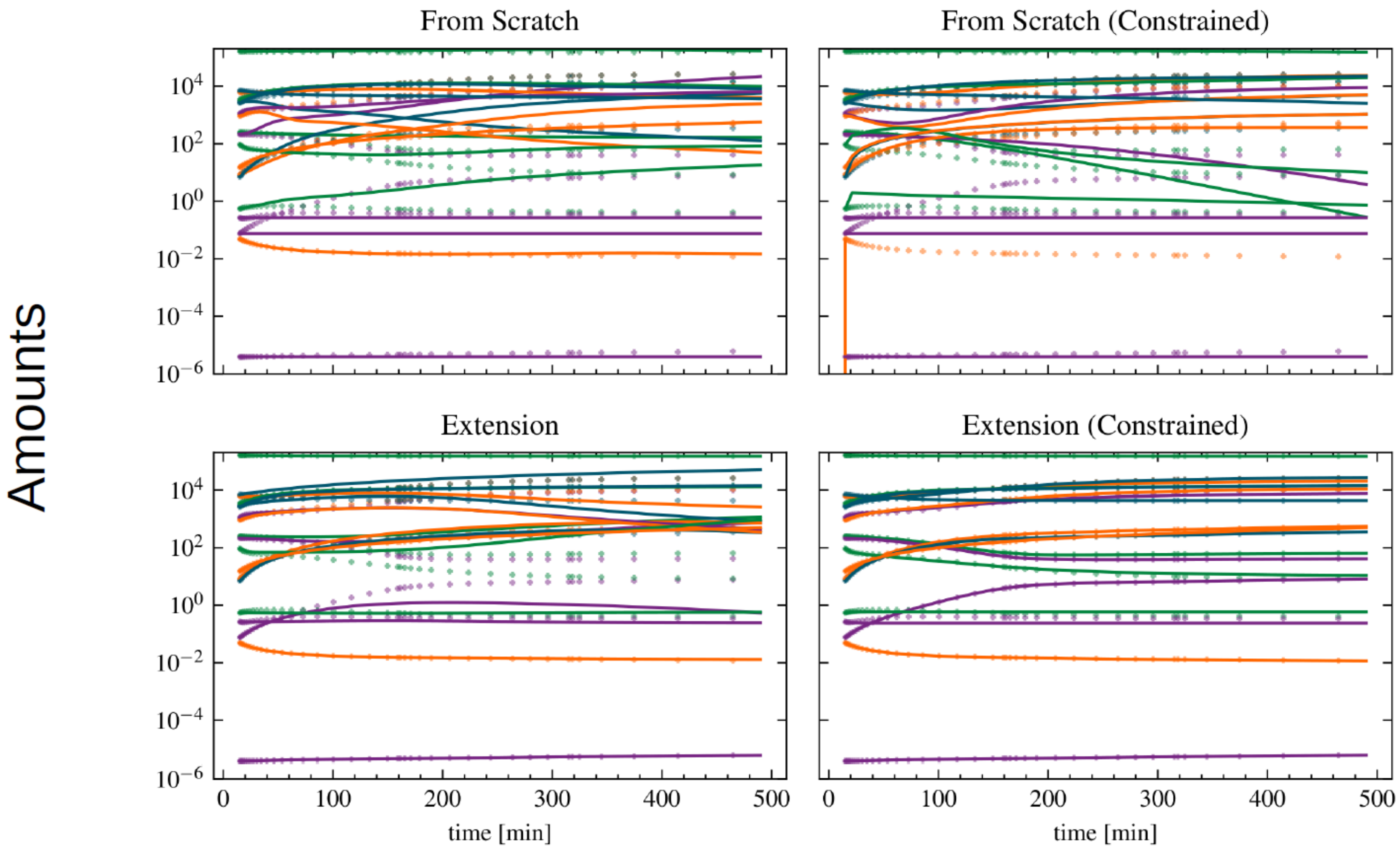
- Biological Interpretability is still an issue, e.g., detours

$$Bcata + NucTCF \xrightarrow{0.00022} NucBcata + NucTCF$$

$$\mathbf{Bcata} \xrightarrow{0.047} \mathbf{NucBcata}$$

Evolving libraries (based on coupled SINDy)

- Improves regression results
- Enables model-level constraints (e.g., each model should have a shuttling event)
- Enables learning of parsimonious models



So you're saying the inevitability of *change* might be a *universal* constant.

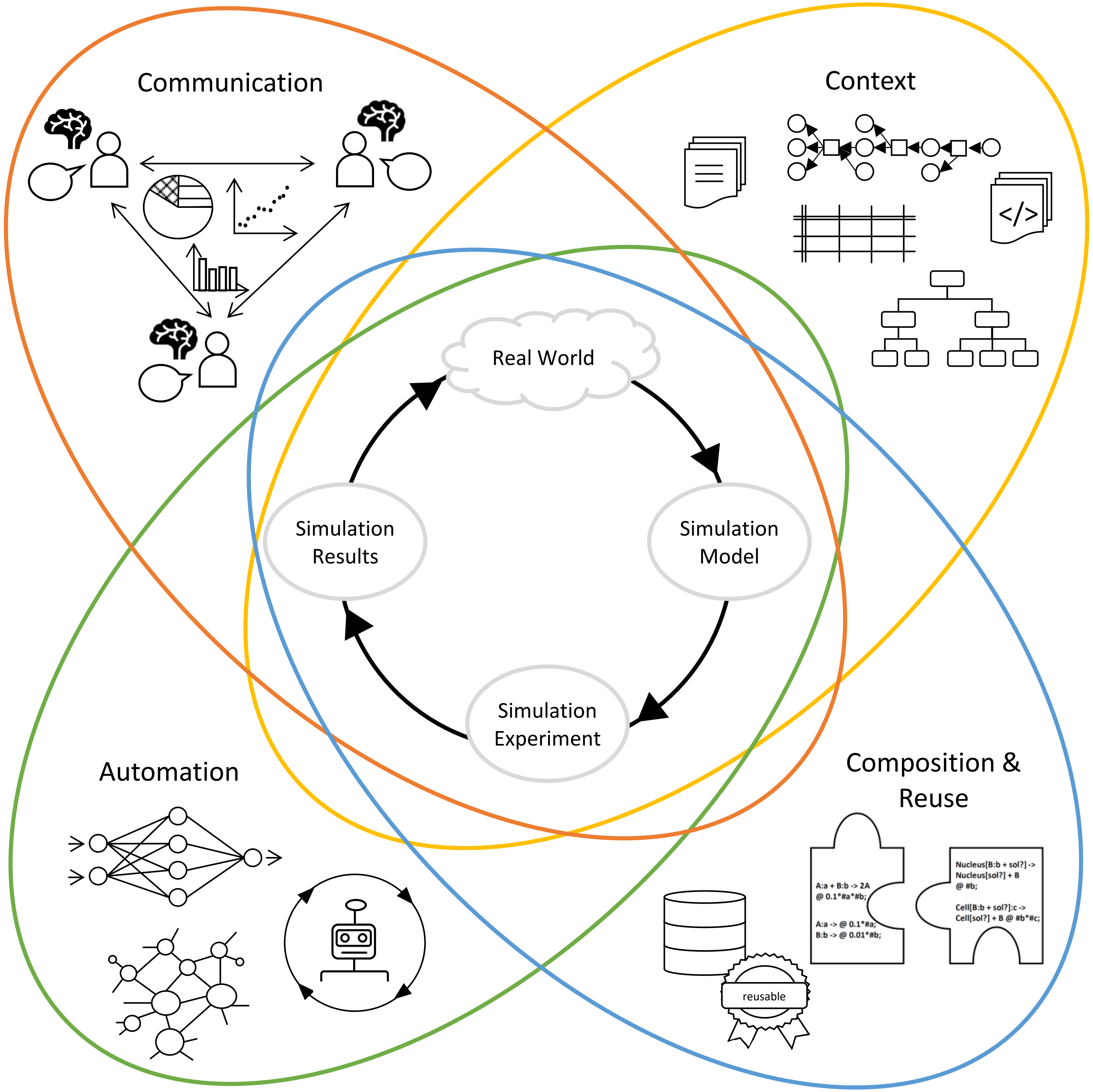
Sheldon

https://www.youtube.com/watch?v=e8my2ZIaKQg

Adaptative simulation models

- Means for communication, e.g., suitable domain-specific modeling languages, and efficient simulators.
- Means for exploiting context, e.g., provenance of adaptation and model lineage
- Means for reuse, e.g., for extending models, reusing simulation experiments
- Means for automation, e.g., generating and executing simulation experiments automatically and learning not only parameters but also (accessible!) model structures

See also: Uhrmacher, A., Frazier, P., Hähnle, R., Klügl, F., Lorig, F., Ludäscher, B., ... & Wilsdorf, P. (2024).
Context, Composition, Automation, and Communication--The C2AC Roadmap for Modeling and Simulation.
TOMACS.



Contributions

Fiete Haack, PhD
biochemical models

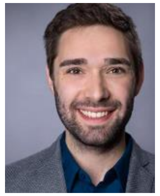
Till Köster
ML-Rules 3,
efficient simulators

Pia Wilsdorf
Automatic generation of experiments,
Provenance

Philipp Henning,
biochemical models

Philipp Andelfinger, PhD
Learning of models,
efficient simulators

Justin Kreikemeyer
Learning of models



Tobias Helms, PhD
Q-learning of
simulators,
ML-Rules 2

Andreas Ruscheinski,
Workflows,
Provenance

Tom Warnke, PhD
ML-Rules 2 + 3
DSLs