Universität Rostock

Traditio et Innovatio

Elaine
electrically active implants
SFB 1270

Modeling long-range Wnt signaling with the domain-specific language ML-Rules

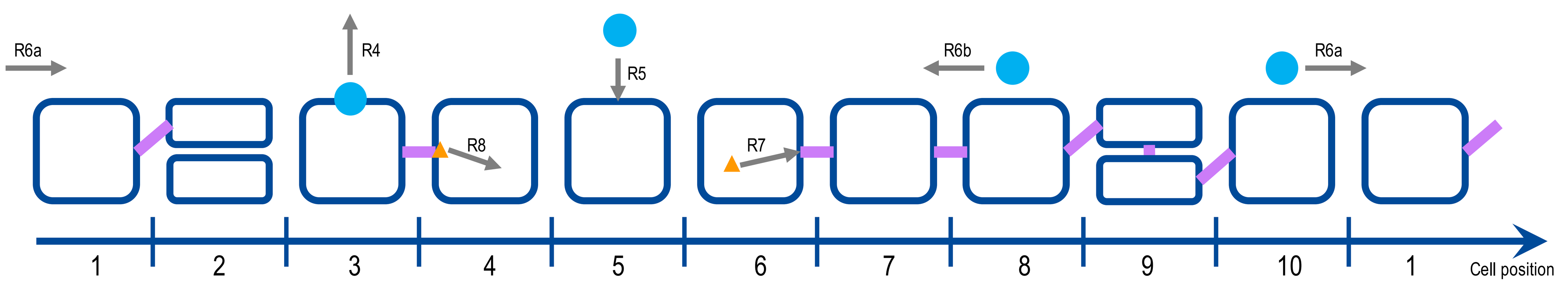
Introduction

Wnt signaling plays a crucial role in embryogenesis and tissue homeostasis [1]. Wnt ligands are lipid-modified proteins and highly hydrophobic. Therefore, they are not subject to free diffusion and it still remains an open question how Wnt signaling is achieved on larger (tissue-) scales. We are presenting a first version of a stochastic model that combines intra- and inter-cellular dynamics of Wnt signaling. The latter considers mechanisms of autocrine and paracrine signaling as well as cross-talk with cadherin signaling [2]. In our model, cells are aligned in a one-dimensional spatial grid and Wnt molecules are being transported within vesicles from one cell to another.

The model has been defined in the domain-specific language ML-Rules [3] and is simulated based on the reaction-diffusion master equation. We illuminate the features of the language that facilitate the definition of compartmental dynamics (e.g., as needed for proliferating cells) and of complex dynamics (e.g., as needed to describe the diffusion of vesicles along neighboring grid cells). Further, we discuss limitations of our model and of the language referring to its spatial accuracy.

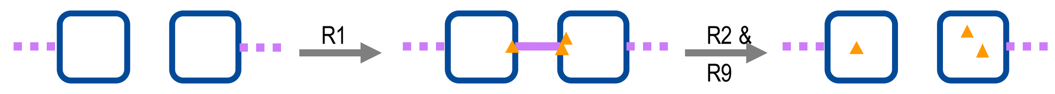
Multi-Scale Model of Long-Range Wnt Signaling

- Periodic grid of cells that may be connected via cadherin junctions and that secrete or absorb vesicles with Wnt molecules

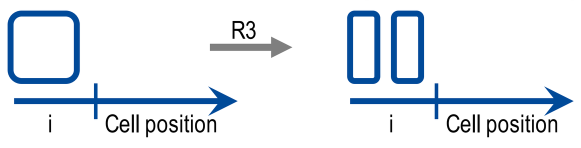


Symbol	Meaning
	Cell
	Nucleus
	Cadherin junction
	Vesicle for Wnt transport
	β-catenin
	Lipid raft

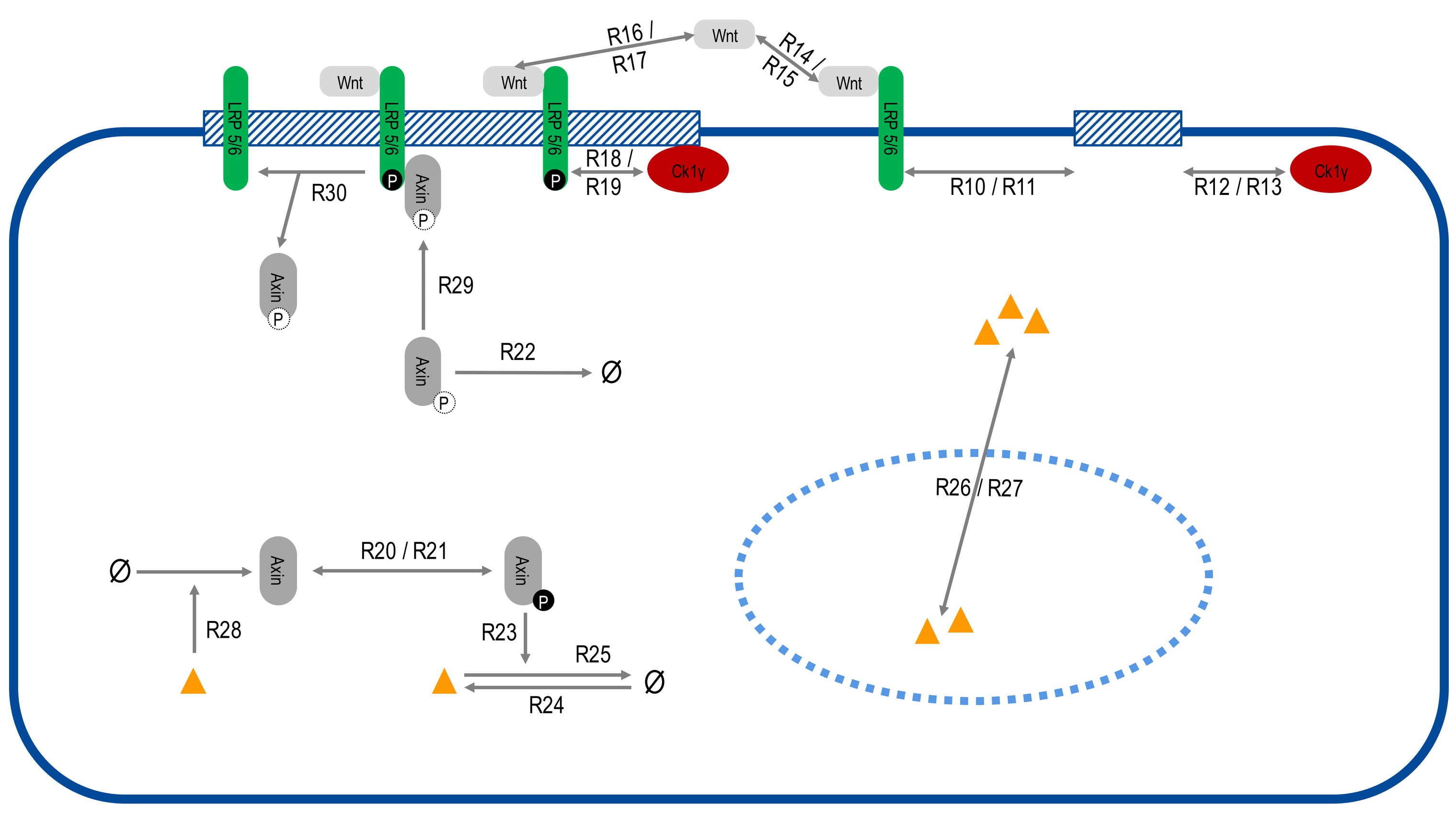
- Two adjacent cells may connect or disconnect with each other through cadherin junctions the cadherin-bound β-catenin is released during disconnection of the junction



- Cells without cadherin junctions may proliferate (new cell is assumed to be in an initial state)



- Intracellular Wnt-model [4]




```
…
// +++++++ Initial and parameter values ++++++++++++++++++++++++++++++++++++++++++++++++
nCells:     5;
…

// +++++++ Functions +++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
// Assign a starting position to every cell at the beginning
positionCells :: num -> sol;
positionCells 0 = [];
positionCells x = standardCell(x, 0) + positionCells(x-1);
…

// +++++++ species definitions (type of attributes) ++++++++++++++++++++++++++++++++++++
Cell(link, link, num)[];    // (left binding partner, right binding partner, position)
Betacat(string);            // ((dis-)connection to cadherin)
…

// +++++++ Initial solution ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
>>INIT[
   positionCells(nCells) +              // Position nCells into grid, one cell per point
   standardCell(nCells + 1, nWnt) +     // Add one standardCell that contains Wnt molecules
   (nCells + 1) Cellcount()             // Dummy variable that counts the cells
];
// +++++++ Reaction Rules ++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
…

// (R2) Cell disconnection through cadherins, all bound beta-catenin is being released
// into the cytoplasm during disconnection -> See (R9)
// (The cells need to be in adjacent grid positions or at the same grid position)
Cell(left, linked, position)[sol1?] + Cell(linked, right, positionNext)[sol2?] ->
Cell(left, free, position)[sol1?] + Cell(free, right, positionNext)[sol2?]
@ if((linked != free) && ((positionNext == position) || (positionNext == (position + 1)))
    ) then k_cadherindiss else 0;

// (R3) Cell proliferation
Cell(free, free, position)[sol1?] -> Cell(free, free, position)[sol1?] +
standardCell(position, 0) + Cellcount @ k_proliferation;
…

// (R6) Diffusion of vesicles with Wnt molecules
// (R6a) Diffusion right
Vesicle(position)[sol?] -> Vesicle(diffuseRight(position))[sol?] @ k_diffusion;
…

// (R7) Beta-catenin connects with cadherin (multiple beta-catenin may connect to one
// cadherin molecule) left side of a cell
Cell(left, right, position)[Betacat('free'):betacat + sol?] ->
Cell(left, right, position)[Betacat('left_bound') + sol?]
@ if(left != free) then (k_cadcatassociation*#betacat) else 0;
…

// (R9) All bound beta-catenin molecules disconnect at once when cell connection is lost
Cell(free, right, position)[Betacat('left_bound') + sol?] ->
Cell(free, right, position)[Betacat('free') + sol?]
@ infinity();
…

// (R30) Dissociation of receptor/Axin complex (signalosome) in LR
Cell(left, right, position)[Membrane[LR[AxinLrp6(phos):la + s_lr?] + s_m?] + s?] ->
Cell(left, right, position)[Membrane[LR[Lrp6('uP', 'uB') + s_lr?] + s_m?] + Axin(phos) +
s?] @(kLA_diss)*#la;
```

Results & Outlook

- ML-Rules enables an effective reuse and composition of existing models implemented in ML-Rules because of the rule metaphor. Bindings and their dynamics can effectively be implemented by using attributed entities and complex rate expressions including conditions.
- ML-Rules enables a succinct and efficient implementation of a multicellular, long-range Wnt signaling model.
- Compartmental dynamics like cell proliferation can naturally be modeled with ML-Rules and they can be tailored by using self-defined functions.
- Missing competition for space leads to an unrestricted cell proliferation.
- Model has to be validated: simulation experiments such as parameter fitting and model checking will be executed.

References

[1] Clevers, H., Loh, K. M., & Nusse, R. (2014). An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. *Science*, *346*(6205), 1248012.

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[3] Helms, T., Warnke, T., Maus, C., & Uhrmacher, A. M. (2017). Semantics and Efficient Simulation Algorithms of an Expressive Multilevel Modeling Language. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, *27*(2), 8.

[4] Haack, F., Lemcke, H., Ewald, R., Rharass, T., & Uhrmacher, A. M. (2015). Spatio-temporal model of endogenous ROS and raft-dependent WNT/beta-catenin signaling driving cell fate commitment in human neural progenitor cells. *PLoS computational biology*, 11(3), e1004106.

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