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A structured approach for the engineering of biochemical network models, illustrated for signalling pathways

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Appendix A: Qualitative and Continuous Petri Nets

The standard notion of qualitative Petri nets, see e.g. [1], are weighted, directed, bipartite graphs with the following basic ingredients.

- There are two types of nodes, which are called places $P = \{p_1, \dots, p_m\}$, in the figures represented by circles, and transitions $T = \{t_1, \dots, t_n\}$, in the figures represented by rectangles. Places usually model passive system components like species, while transitions stand for active system components like reactions.
- The directed arcs connect always nodes of different type.
- Arcs are weighted by natural numbers. The arc weight may be read as the multiplicity of the arc, reflecting known stoichiometries. The arc weight 1 is the default value and is usually not given explicitly.
- A place carries an arbitrary number of tokens, represented as black dots or a natural number. The number zero is the default value and usually not given explicitly. Tokens can be interpreted as the available amount of a given species in number of molecules or moles, or any abstract, i.e. discrete concentration level.

The tokens on all places establish the marking of the net, which represents the current state of the system.

The tokens may move through the net driven by the firing of transitions. The rules of the token game are defined by the firing rule. It consists of two parts: the precondition and the firing itself.

- A transition is *enabled*, if all its preplaces carry at least as many tokens as required by the weights of the corresponding ingoing arcs.
- An enabled transition *may* fire, i.e. a transition is never forced to fire. The firing of a transition removes from all its preplaces as many tokens as specified by the ingoing arc weights, and adds to all its postplaces as many tokens as specified by the outgoing arc weights. The firing happens atomically and does not consume any time.

The repeated atomic firing of transitions establishes the discrete behaviour of the qualitative Petri net.

Continuous Petri nets are a quantified version of this standard notion of qualitative Petri nets. Like their ancestor, they are weighted, directed, bipartite graphs, however arc weights and the numbers assigned to places are now non-negative real numbers. Thus, the number of tokens on each place is replaced by a token value, which we interpret as the concentration of a given species. The instantaneous firing of a continuous transition is carried out like a continuous flow, whereby the strength of the flow is determined by a firing rate function, which each transition gets assigned.

To be precise we give the following definition of biochemically interpreted continuous Petri nets.

Definition 0.1 (Continuous Petri net) A continuous Petri net is a quintuple $\mathcal{CON} = \langle P, T, f, v, m_0 \rangle$, where

- P and T are finite, non empty, and disjoint sets. P is the set of continuous places. T is the set of continuous transitions.
- $f : ((P \times T) \cup (T \times P)) \rightarrow \mathbf{R}_0^+$ defines the set of directed arcs, weighted by non-negative real numbers.
- $v : T \rightarrow H$ assigns to each transition a firing rate function, whereby $H := \bigcup_{t \in T} \{h_t | h_t : \mathbf{R}^{|\bullet t|} \rightarrow \mathbf{R}\}$ is the set of all firing rate functions, and $v(t) = h_t$ for all transitions $t \in T$.
- $m_0 : P \rightarrow \mathbf{R}_0^+$ gives the initial marking.

The function $v(t)$ defines the marking-dependent transition rate for the transition t . The domain of $v(t)$ is restricted to the set of pre-places of t , i.e. $\bullet t := \{p \in P | f(p, t) \neq 0\}$, to enforce a close relation between network structure and transition rate functions. Therefore $v(t)$ actually depends only on a sub-marking. Technically, any mathematical function in compliance with this restriction is allowed for $v(t)$. However, often special kinetic patterns are applied, whereby Michaelis-Menten and mass-action kinetics seem to be the most popular ones.

The behaviour of a continuous Petri net is defined by the following. A continuous transition t is enabled at m , iff $\forall p \in \bullet t : m(p) > 0$. Due to the influence of time, a continuous transition is forced to fire as soon as possible.

Altogether, the semantics of a continuous Petri net is defined by a system of ordinary differential equations (ODEs), where one equation describes the continuous change over time on the token value of a given place by the continuous increase of its pre-transitions' flow and the continuous decrease of its post-transitions' flow, i.e., each place p subject to changes gets its own equation:

$$\frac{dm(p)}{dt} = \sum_{t \in \bullet p} f(t, p) v(t) - \sum_{t \in p^\bullet} f(p, t) v(t).$$

The notation $\bullet p$ specifies the set of pre-transitions of p , i.e. all reactions producing the species p : $\bullet p := \{t \in T | f(t, p) \neq 0\}$, and $p^\bullet$ specifies the set of post-transitions of p , i.e. all reactions consuming the species p : $p^\bullet := \{t \in T | f(p, t) \neq 0\}$.

The notation $m(p)$ refers to the current token value of place p , and corresponds to the more popular notation $[p]$. To simplify the notation in the generated ODEs, places are usually interpreted as (non-negative) real variables, which allows to write, e.g., $v(A, B)$ instead of $v(m(A), m(B))$ or $v([A], [B])$.

Each equation corresponds basically to a line in the incidence matrix (stoichiometric matrix), whereby now the matrix elements consist of the rate functions multiplied by the arc weight, if any. Moreover, as soon as there are transitions with more than one pre-place, we get typically a non-linear system, which calls for a numerical treatment of the system on hand.

With other words, the continuous Petri net becomes the structured description of the corresponding ODEs. Due to the explicit structure we expect to get descriptions which are less error prone compared to those ones created manually in a textual notation from the scratch. For more details see [2], and for a family of related models see [3].

Appendix B: Complete Example Nets

In the following we give six models of a three-stage signalling cascade, demonstrating the composition principle using building blocks. First, the basic models for in vivo and in vitro cascades are given, each extended afterwards by negative feedback (according to the pattern given in Figure 12(a)) and drug inhibition.

The given Petri nets may be read as discrete as well as continuous ones. The essential analysis results of the discrete Petri nets are given directly below the net in the style of the two-column result vector as produced by the Integrated Net Analyser INA [4]. By assigning rate functions, the Petri nets turn into continuous ones, describing ODEs. Please note, here we read the place names as real variables, which allows to skip the bracket notation, which is usually used to indicate that the species' concentration is meant and not the species itself. All ODEs are given as produced by Snoopy [5], a tool to design and animate hierarchical graphs, especially Petri nets.

References

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- [5] Snoopy. A tool to design and animate hierarchical graphs. BTU Cottbus, CS Dep., www-dssz.informatik.tu-cottbus.de.

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	Y
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
Y	Y	Y	Y	Y	Y	Y	Y	Y	N	?	N	N	Y	Y	Y	

 7 p-invariants
 9 t-invariants (6 trivial, 3 non-trivial)
 rg: 43 states, 156 arcs, 1 scc

Figure 1: Three-stage in vivo cascade (MA1).

ODEs generated by the continuous Petri net given in Figure 1

$$\begin{aligned}
\frac{dP1}{dt} &= kr3 * Rp|P1 + kr2 * Rp|P1 - kr1 * Rp * P1 \\
\frac{dP2}{dt} &= kkr3 * RRp|P2 + kkr2 * RRp|P2 - kkr1 * RRp * P2 \\
\frac{dP3}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRRp|P3 - kkk1 * RRRp * P3 \\
\frac{dR}{dt} &= kr3 * Rp|P1 + k2 * R|S1 - k1 * R * S1 \\
\frac{dRR}{dt} &= kkr3 * RRp|P2 + kk2 * RR|Rp - kk1 * RR * Rp \\
\frac{dRRR}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRR|RRp - kkk1 * RRR * RRp \\
\frac{dRRRp}{dt} &= kkk3 * RRR|RRp + kkk2 * RRRp|P3 - kkk1 * RRRp * P3 \\
\frac{dRRRp|P3}{dt} &= kkk1 * RRRp * P3 - kkk3 * RRRp|P3 - kkk2 * RRRp|P3 \\
\frac{dRRR|RRp}{dt} &= kkk1 * RRR * RRp - kkk3 * RRR|RRp - kkk2 * RRR|RRp \\
\frac{dRRp}{dt} &= kk3 * RR|Rp + kkk3 * RRR|RRp + kkr2 * RRp|P2 + \\
&\quad kkk2 * RRR|RRp - kkr1 * RRp * P2 - kkk1 * RRR * RRp \\
\frac{dRRp|P2}{dt} &= kkr1 * RRp * P2 - kkr3 * RRp|P2 - kkr2 * RRp|P2 \\
\frac{dRR|Rp}{dt} &= kk1 * RR * Rp - kk3 * RR|Rp - kk2 * RR|Rp \\
\frac{dRp}{dt} &= k3 * R|S1 + kk3 * RR|Rp + kr2 * Rp|P1 + kk2 * RR|Rp - \\
&\quad kr1 * Rp * P1 - kk1 * RR * Rp \\
\frac{dRp|P1}{dt} &= kr1 * Rp * P1 - kr3 * Rp|P1 - kr2 * Rp|P1 \\
\frac{dR|S1}{dt} &= k1 * R * S1 - k3 * R|S1 - k2 * R|S1 \\
\frac{dS1}{dt} &= k3 * R|S1 + k2 * R|S1 - k1 * R * S1
\end{aligned}$$

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	N	N	Y	Y	Y
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
N	Y	N	N	Y	N	Y	Y	N	Y	?	N	N	N	N	N	

 4 p-invariants
 3 trivial t-invariants
 rg: 7 states, 9 arcs, 4 scc's

Figure 2: Three-stage in vitro cascade (MA1).

ODEs generated by the continuous Petri net given in Figure 2

$$\frac{dR}{dt} = k_2 * R|S_1 - k_1 * R * S_1$$

$$\frac{dRR}{dt} = kk_2 * RR|Rp - kk_1 * RR * Rp$$

$$\frac{dRRR}{dt} = kkk_2 * RRR|RRp - kkk_1 * RRR * RRp$$

$$\frac{dRRRp}{dt} = kkk_3 * RRR|RRp$$

$$\frac{dRRR|RRp}{dt} = kkk_1 * RRR * RRp - kkk_3 * RRR|RRp - kkk_2 * RRR|RRp$$

$$\frac{dRRp}{dt} = kk_3 * RR|Rp + kkk_3 * RRR|RRp + kkk_2 * RRR|RRp - kkk_1 * RRR * RRp$$

$$\frac{dRR|Rp}{dt} = kk_1 * RR * Rp - kk_3 * RR|Rp - kk_2 * RR|Rp$$

$$\frac{dRp}{dt} = k_3 * R|S_1 + kk_3 * RR|Rp + kk_2 * RR|Rp - kk_1 * RR * Rp$$

$$\frac{dR|S_1}{dt} = k_1 * R * S_1 - k_3 * R|S_1 - k_2 * R|S_1$$

$$\frac{dS_1}{dt} = k_3 * R|S_1 + k_2 * R|S_1 - k_1 * R * S_1$$

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
Y	Y	Y	N	Y	Y	Y	Y	Y	N	?	N	N	Y	Y	Y	

```

7 p-invariants
10 t-invariants (7 trivial, 3 non-trivial)
rg: 53 states, 197 arcs, 1 scc

```

Figure 3: Three-stage in vivo cascade with negative feedback (MA1).

ODEs generated by the continuous Petri net given in Figure 3

$$\begin{aligned}
\frac{dP1}{dt} &= kr3 * Rp|P1 + kr2 * Rp|P1 - kr1 * Rp * P1 \\
\frac{dP2}{dt} &= kkr3 * RRp|P2 + kkr2 * RRp|P2 - kkr1 * RRp * P2 \\
\frac{dP3}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRRp|P3 - kkk1 * RRRp * P3 \\
\frac{dR}{dt} &= kr3 * Rp|P1 + k2 * R|S1 - k1 * R * S1 \\
\frac{dRR}{dt} &= kkr3 * RRp|P2 + kk2 * RR|Rp - kk1 * RR * Rp \\
\frac{dRRR}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRR|RRp - kkk1 * RRR * RRp \\
\frac{dRRRp}{dt} &= kkk3 * RRR|RRp + kkk2 * RRRp|P3 + i2 * S1|RRRp - \\
&\quad kkk1 * RRRp * P3 - i1 * S1 * RRRp \\
\frac{dRRRp|P3}{dt} &= kkk1 * RRRp * P3 - kkk3 * RRRp|P3 - kkk2 * RRRp|P3 \\
\frac{dRRR|RRp}{dt} &= kkk1 * RRR * RRp - kkk3 * RRR|RRp - kkk2 * RRR|RRp \\
\frac{dRRp}{dt} &= kk3 * RR|Rp + kkk3 * RRR|RRp + kkr2 * RRp|P2 + \\
&\quad kkk2 * RRR|RRp - kkr1 * RRp * P2 - kkk1 * RRR * RRp \\
\frac{dRRp|P2}{dt} &= kkr1 * RRp * P2 - kkr3 * RRp|P2 - kkr2 * RRp|P2 \\
\frac{dRR|Rp}{dt} &= kk1 * RR * Rp - kk3 * RR|Rp - kk2 * RR|Rp \\
\frac{dRp}{dt} &= k3 * R|S1 + kk3 * RR|Rp + kr2 * Rp|P1 + kk2 * RR|Rp - \\
&\quad kr1 * Rp * P1 - kk1 * RR * Rp \\
\frac{dRp|P1}{dt} &= kr1 * Rp * P1 - kr3 * Rp|P1 - kr2 * Rp|P1 \\
\frac{dR|S1}{dt} &= k1 * R * S1 - k3 * R|S1 - k2 * R|S1 \\
\frac{dS1}{dt} &= k3 * R|S1 + k2 * R|S1 + i2 * S1|RRRp - k1 * R * S1 - \\
&\quad i1 * S1 * RRRp \\
\frac{dS1|RRRp}{dt} &= i1 * S1 * RRRp - i2 * S1|RRRp
\end{aligned}$$

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	Y
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
N	?	N	N	Y	N	Y	Y	N	N	?	N	N	N	N	N	

 4 p-invariants
 4 trivial t-invariants
 rg: 8 states, 11 arcs, 4 scc's

Figure 4: Three-stage in vitro cascade with negative feedback (MA1).

ODEs generated by the continuous Petri net given in Figure 4

$$\begin{aligned}
\frac{dR}{dt} &= k_2 * R|S_1 - k_1 * R * S_1 \\
\frac{dRR}{dt} &= kk_2 * RR|Rp - kk_1 * RR * Rp \\
\frac{dRRR}{dt} &= kkk_2 * RRR|RRp - kkk_1 * RRR * RRp \\
\frac{dRRRp}{dt} &= kkk_3 * RRR|RRp + i_2 * S_1|RRRp - i_1 * S_1 * RRRp \\
\frac{dRRR|RRp}{dt} &= kkk_1 * RRR * RRp - kkk_3 * RRR|RRp - kkk_2 * RRR|RRp \\
\frac{dRRp}{dt} &= kk_3 * RR|Rp + kkk_3 * RRR|RRp + kkk_2 * RRR|RRp - \\
&\quad kkk_1 * RRR * RRp \\
\frac{dRR|Rp}{dt} &= kk_1 * RR * Rp - kk_3 * RR|Rp - kk_2 * RR|Rp \\
\frac{dRp}{dt} &= k_3 * R|S_1 + kk_3 * RR|Rp + kk_2 * RR|Rp - kk_1 * RR * Rp \\
\frac{dR|S_1}{dt} &= k_1 * R * S_1 - k_3 * R|S_1 - k_2 * R|S_1 \\
\frac{dS_1}{dt} &= k_3 * R|S_1 + k_2 * R|S_1 + i_2 * S_1|RRRp - k_1 * R * S_1 - \\
&\quad i_1 * S_1 * RRRp \\
\frac{dS_1|RRRp}{dt} &= i_1 * S_1 * RRRp - i_2 * S_1|RRRp
\end{aligned}$$

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
Y	Y	Y	N	Y	Y	Y	Y	Y	N	?	N	N	Y	Y	Y	

8 p-invariants
 17 t-invariants (11 trivial, 6 non-trivial)
 rg: 102 states, 436 arcs, 1 scc

Figure 5: Three-stage in vivo cascade with negative feedback and drug inhibition (MA1). The nodes given in gray indicate logical nodes (also called fusion nodes). Logical nodes with identical names are from a structural point of view identical; they are used to increase readability in larger net structures by connecting logically remote net parts.

ODEs generated by the continuous Petri net given in Figure 5

$$\begin{aligned}
\frac{dP1}{dt} &= kr3 * Rp|P1 + kr2 * Rp|P1 - kr1 * Rp * P1 \\
\frac{dP2}{dt} &= kkr3 * RRp|P2 + kkr2 * RRp|P2 + kkr3u * RRp|P2|U + \\
&\quad kkr2u * RRp|P2|U - kkr1 * RRp * P2 - kkr1u * RRp|U * P2 \\
\frac{dP3}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRRp|P3 - kkk1 * RRRp * P3 \\
\frac{dR}{dt} &= kr3 * Rp|P1 + k2 * R|S1 - k1 * R * S1 \\
\frac{dRR}{dt} &= kkr3 * RRp|P2 + kk2 * RR|Rp + u1u * RR|U - kk1 * RR * Rp - \\
&\quad b1u * RR * U \\
\frac{dRRR}{dt} &= kkk3 * RRRp|P3 + kkk2 * RRR|RRp - kkk1 * RRR * RRp \\
\frac{dRRRp}{dt} &= kkk3 * RRR|RRp + kkk2 * RRRp|P3 + i2 * S1|RRRp - \\
&\quad kkk1 * RRRp * P3 - i1 * S1 * RRRp \\
\frac{dRRRp|P3}{dt} &= kkk1 * RRRp * P3 - kkk3 * RRRp|P3 - kkk2 * RRRp|P3 \\
\frac{dRRR|RRp}{dt} &= kkk1 * RRR * RRp - kkk3 * RRR|RRp - kkk2 * RRR|RRp \\
\frac{dRRp}{dt} &= kk3 * RR|Rp + kkk3 * RRR|RRp + kkr2 * RRp|P2 + kkk2 * RRR|RRp + \\
&\quad u2u * RRp|U - kkr1 * RRp * P2 - kkk1 * RRR * RRp - b2u * RRp * U \\
\frac{dRRp|P2}{dt} &= kkr1 * RRp * P2 - kkr3 * RRp|P2 - kkr2 * RRp|P2 \\
\frac{dRRp|P2|U}{dt} &= kkr1u * RRp|U * P2 - kkr3u * RRp|P2|U - kkr2u * RRp|P2|U \\
\frac{dRRp|U}{dt} &= kk3u * RR|Rp|U + b2u * RRp * U + kkr2u * RRp|P2|U - u2u * RRp|U - \\
&\quad kkr1u * RRp|U * P2 \\
\frac{dRR|Rp}{dt} &= kk1 * RR * Rp - kk3 * RR|Rp - kk2 * RR|Rp \\
\frac{dRR|Rp|U}{dt} &= kk1u * RR|U * Rp - kk3u * RR|Rp|U - kk2u * RR|Rp|U \\
\frac{dRR|U}{dt} &= b1u * RR * U + kkr3u * RRp|P2|U + kk2u * RR|Rp|U - u1u * RR|U - \\
&\quad kk1u * RR|U * Rp \\
\frac{dRp}{dt} &= k3 * R|S1 + kk3 * RR|Rp + kr2 * Rp|P1 + kk2 * RR|Rp + \\
&\quad kk2u * RR|Rp|U + kk3u * RR|Rp|U - kr1 * Rp * P1 - kk1 * RR * Rp - \\
&\quad kk1u * RR|U * Rp \\
\frac{dRp|P1}{dt} &= kr1 * Rp * P1 - kr3 * Rp|P1 - kr2 * Rp|P1 \\
\frac{dR|S1}{dt} &= k1 * R * S1 - k3 * R|S1 - k2 * R|S1 \\
\frac{dS1}{dt} &= k3 * R|S1 + k2 * R|S1 + i2 * S1|RRRp - k1 * R * S1 - i1 * S1 * RRRp \\
\frac{dS1|RRRp}{dt} &= i1 * S1 * RRRp - i2 * S1|RRRp \\
\frac{dU}{dt} &= u1u * RR|U + u2u * RRp|U - b1u * RR * U - b2u * RRp * U
\end{aligned}$$

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S	
N	Y	N	N	Y	N	Y	Y	N	N	?	N	N	N	N	N	

 5 p-invariants
 7 trivial t-invariants
 rg: 15 states, 31 arcs, 4 scc's

Figure 6: Three-stage in vitro cascade with negative feedback and drug inhibition (MA1).

ODEs generated by the continuous Petri net given in Figure 6

$$\begin{aligned}
\frac{dR}{dt} &= k_2 * R|S_1 - k_1 * R * S_1 \\
\frac{dRR}{dt} &= kk_2 * RR|Rp + u_{1u} * RR|U - kk_1 * RR * Rp - b_{1u} * RR * U \\
\frac{dRRR}{dt} &= kkk_2 * RRR|RRp - kkk_1 * RRR * RRp \\
\frac{dRRRp}{dt} &= kkk_3 * RRR|RRp + i_2 * S_1|RRRp - i_1 * S_1 * RRRp \\
\frac{dRRR|RRp}{dt} &= kkk_1 * RRR * RRp - kkk_3 * RRR|RRp - kkk_2 * RRR|RRp \\
\frac{dRRp}{dt} &= kk_3 * RR|Rp + kkk_3 * RRR|RRp + kkk_2 * RRR|RRp + \\
&\quad u_{2u} * RRp|U - kkk_1 * RRR * RRp - b_{2u} * RRp * U \\
\frac{dRRp|U}{dt} &= kk_3u * RR|Rp|U + b_{2u} * RRp * U - u_{2u} * RRp|U \\
\frac{dRR|Rp}{dt} &= kk_1 * RR * Rp - kk_3 * RR|Rp - kk_2 * RR|Rp \\
\frac{dRR|Rp|U}{dt} &= kk_1u * RR|U * Rp - kk_3u * RR|Rp|U - kk_2u * RR|Rp|U \\
\frac{dRR|U}{dt} &= b_{1u} * RR * U + kk_{2u} * RR|Rp|U - u_{1u} * RR|U - \\
&\quad kk_{1u} * RR|U * Rp \\
\frac{dRp}{dt} &= k_3 * R|S_1 + kk_3 * RR|Rp + kk_2 * RR|Rp + kk_{2u} * RR|Rp|U + \\
&\quad kk_{3u} * RR|Rp|U - kk_1 * RR * Rp - kk_{1u} * RR|U * Rp \\
\frac{dR|S_1}{dt} &= k_1 * R * S_1 - k_3 * R|S_1 - k_2 * R|S_1 \\
\frac{dS_1}{dt} &= k_3 * R|S_1 + k_2 * R|S_1 + i_2 * S_1|RRRp - k_1 * R * S_1 - \\
&\quad i_1 * S_1 * RRRp \\
\frac{dS_1|RRRp}{dt} &= i_1 * S_1 * RRRp - i_2 * S_1|RRRp \\
\frac{dU}{dt} &= u_{1u} * RR|U + u_{2u} * RRp|U - b_{1u} * RR * U - b_{2u} * RRp * U
\end{aligned}$$