Bio-PEPA for epidemiological models

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Epidemiological models

Epidemiological models study the spread of disease within a population.

For this purpose the population can be divided into classes: susceptibles (S), those who are infective (I) and those who have recovered (R) and are immune.

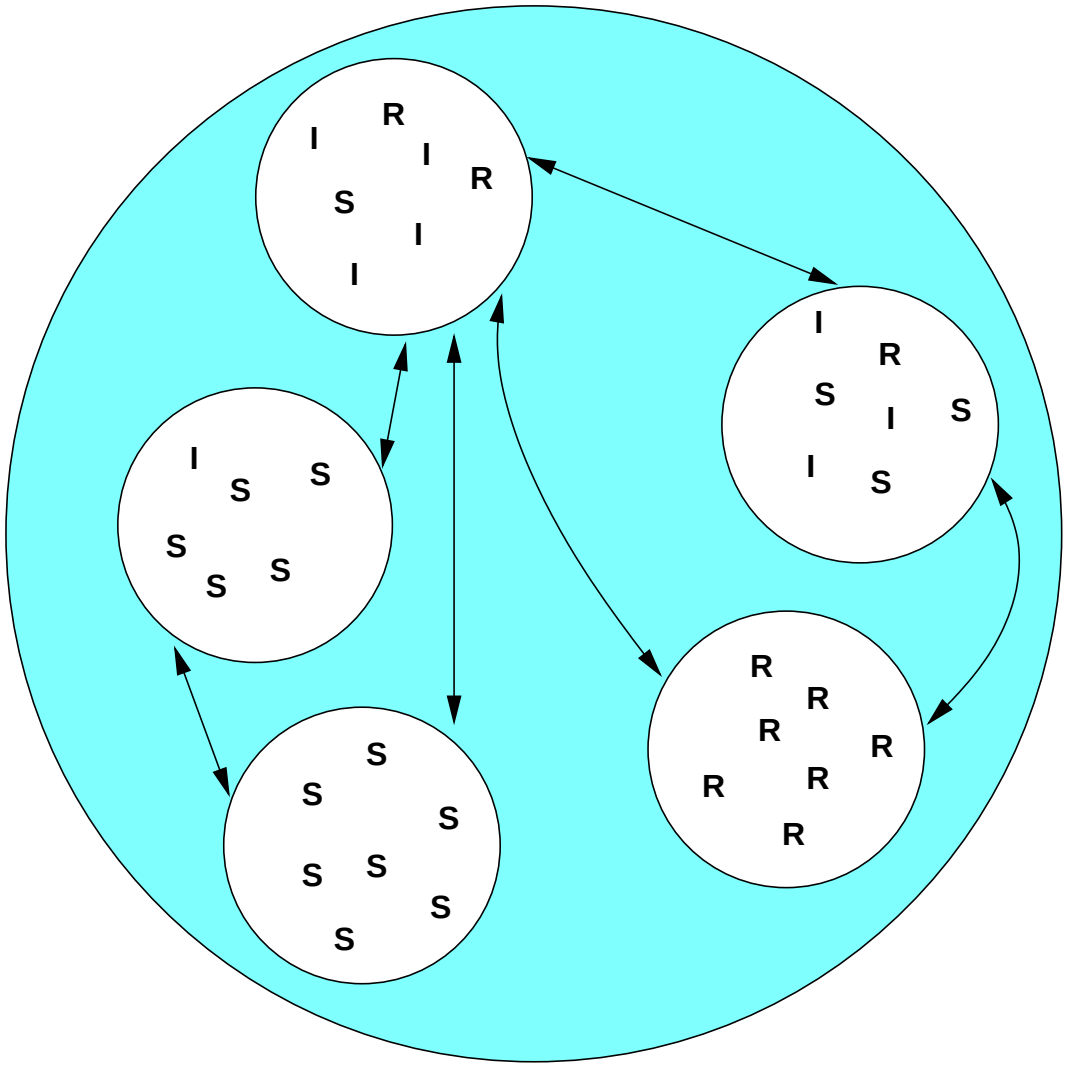
Refinements of this might include differentiating those which are symptomatic or asymptomatic, treated or untreated, or suffering from a drug-resistant form of the disease.

Furthermore, dynamics within the population such as births and deaths can also play a role in the spread of the disease.

Spatial structures

- Spatial structure can have a large impact on the evolution of a population and particularly on the outcome of a disease.
- Generally an abstract view of space is sufficient to describe the spatial evolution of the epidemic.
- The term metapopulation is used to indicate a population distributed over a number of patches or subpopulations, i.e. groups of individuals in the model.
- Individuals can migrate from one patch to another and this can be described by a migration matrix $M(i, j)$, that determines the topology and the strength of the connections between the patches.

Passing on infection



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- The local states of components are quantitative rather than functional, i.e. distinct states of the species are represented as distinct components, not derivatives of a single component.
- There is a notion of location within models intended to capture the compartments and membranes which physically divide the space within a cell.

Using Bio-PEPA for epidemiological models

- Each species will correspond to a subset of individuals (e.g. susceptible, infective or recovered individuals).
- The role of the individual with respect to an action does not have the significance that it does in biochemistry, but can be used to indicate that the species decreases, remains invariant or increases in an interaction.
- Interactions such as $I + S \rightarrow 2I$ are possible, where an entity is present on both sides of the interaction with different multiplicity. Note that this cannot be represented in Bio-PEPA.
- While spatial structures are often present in epidemiological models here it is meaningless to distinguish membranes and compartments.

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The abstraction

The translation of epidemiological models into Bio-PEPA is based on the following correspondences:

- Each subpopulation/patch is abstracted by a location.
- Each species is represented by a species component, whose subterms describe its interaction capabilities.
- Each interaction is represented by an action type. The dynamics are described by a functional rate.
- The model component represents how the species interact and contains information about the initial state.

Models of H5N1 Avian Influenza

- We constructed a number of Bio-PEPA models of growing sophistication of the spread of the H5N1 Avian Influenza.
- The Bio-PEPA Workbench was used for analysis.
- This involved generating both continuous (ODE) and discrete simulations using the Dizzy simulation engine.
- Stochastic simulations were replicated 100 times.
- Additionally in some cases we generated PRISM models and verified properties using stochastic model checking.
- Results were validated against previously published results of hand-crafted ODEs and stochastic simulations [Debarre et al, Ecology 2007].

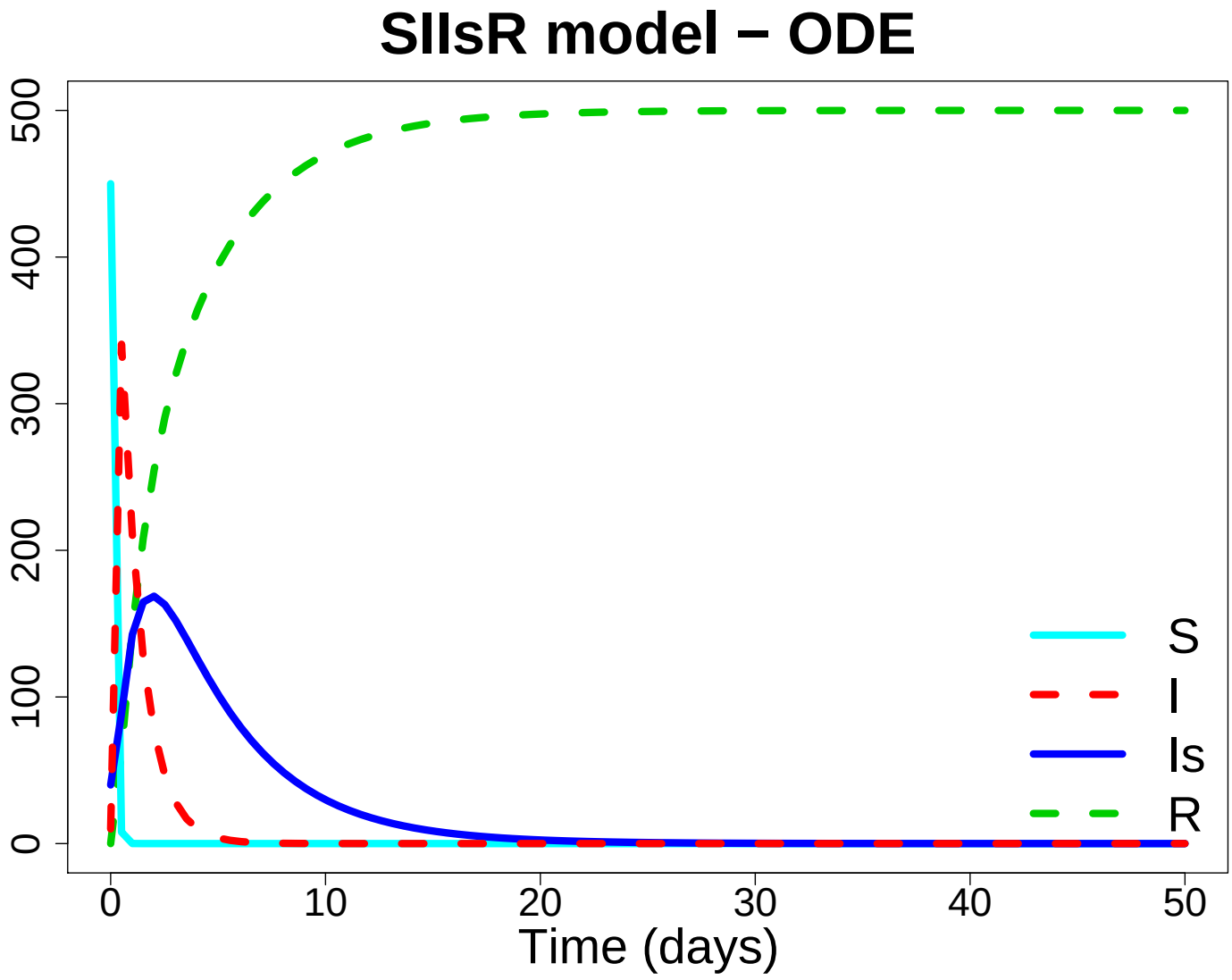
Simple model: single location, no drug treatment

We distinguish between asymptomatic (I) and symptomatic (I_s) individuals:

$$
\begin{aligned}
S &\stackrel{def}{=} (contact1,1)\downarrow S + (contact2,1)\downarrow S \\
I &\stackrel{def}{=} (contact1,(1,2)) \odot I + (contact2,1)\uparrow I \\
&\quad + \ (recovery1,1)\downarrow I + (symp,1)\downarrow I \\
I_s &\stackrel{def}{=} (contact2,(1,1)) \odot I_s + (recovery2,1)\downarrow I_s + (symp,1)\uparrow I_s \\
R &\stackrel{def}{=} (recovery1,1)\uparrow R + (recovery2,1)\uparrow R
\end{aligned}
$$

$$
S(450) \underset{*}{\bowtie} I(10) \underset{*}{\bowtie} I_s(40) \underset{*}{\bowtie} R(0)
$$

Simulation Results



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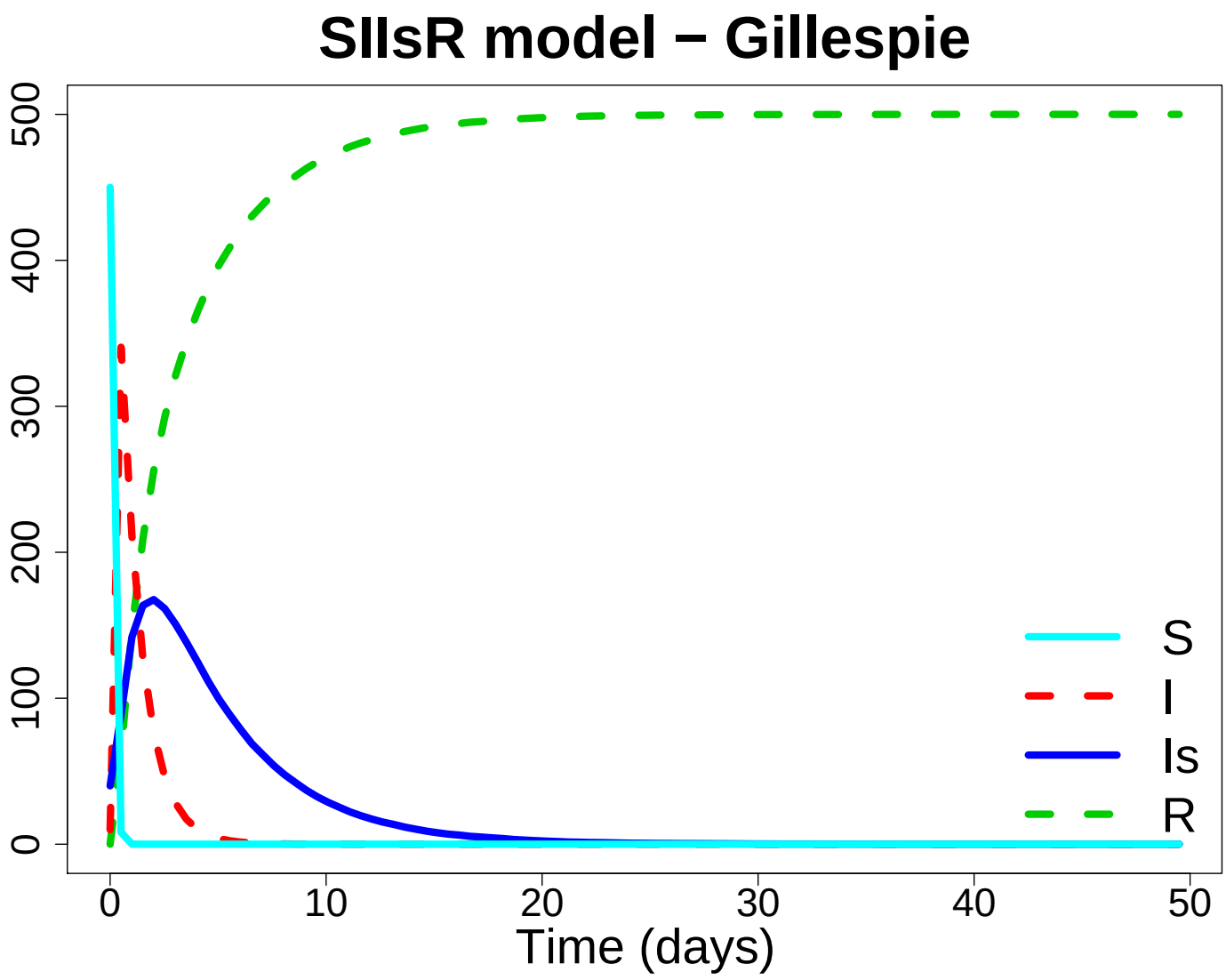

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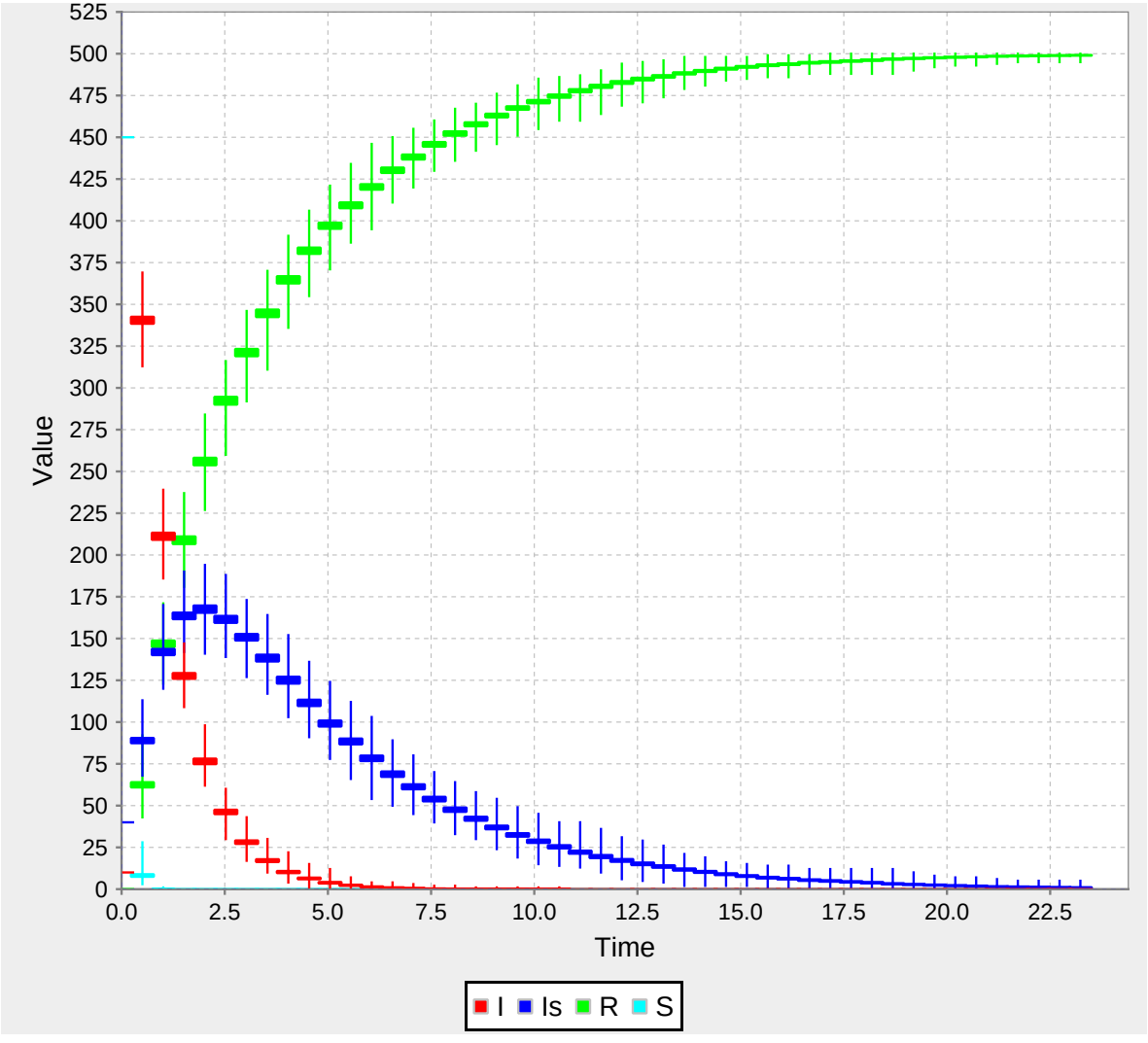
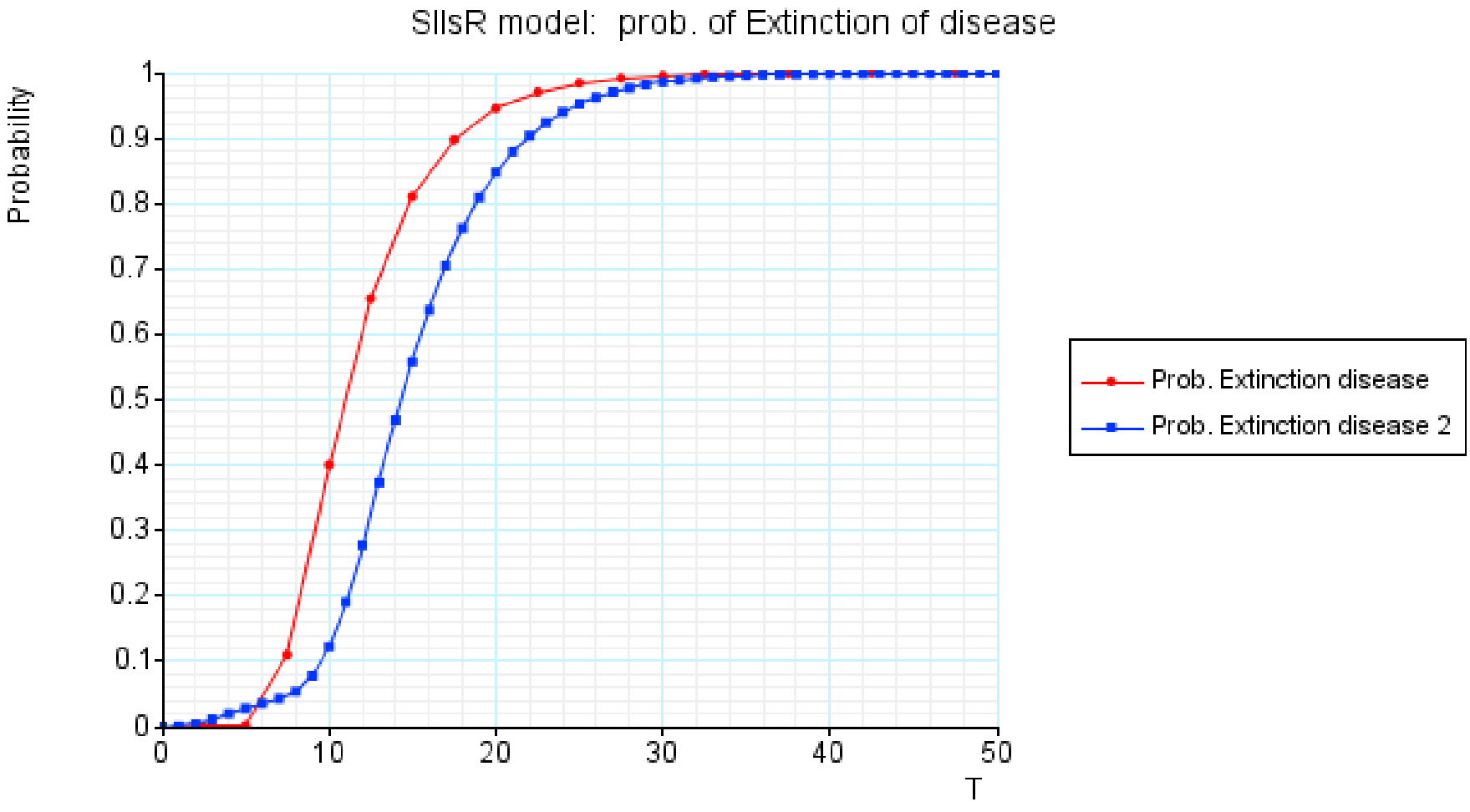


PRISM Results — Varying contact rates



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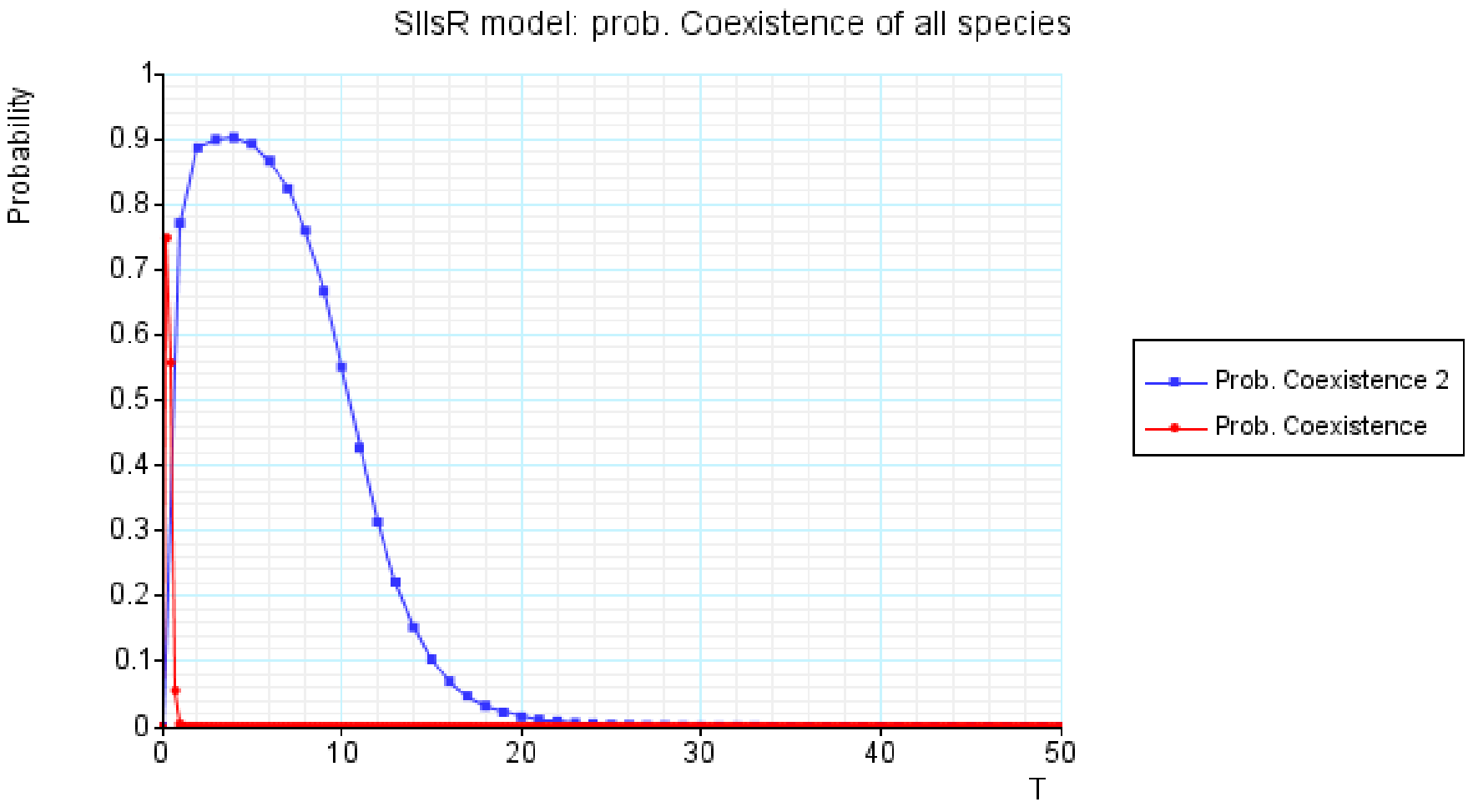

Models with multiple locations

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Five locations are used and the initial population of 500 is split evenly. Initially only one patch contains infected individuals.

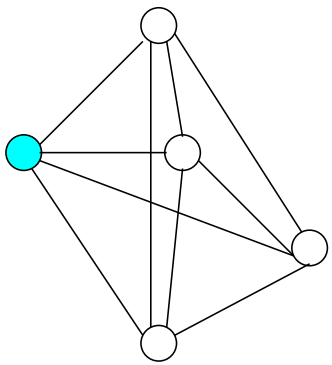
Interactions between individuals are as in the previous model but constrained to only occur when they are in the same location. Additionally there are migration actions, e.g:

$$S \stackrel{def}{=} (contact1, 1)\downarrow S + (contact2, 1)\downarrow S + \sum_{M(i,j)\neq 0} (m_{ij,S}[location\_i \rightarrow location\_j], (1,1)) \odot S$$

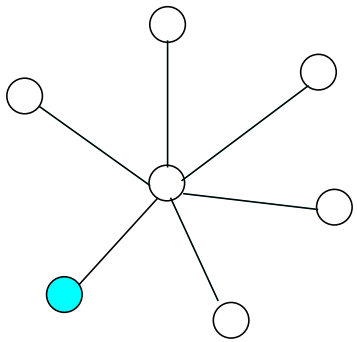
The action types *contactj*, $j = 1, 2$, abstract the action types *contactj@location_i*, with $i = 1, ..., 5$

Population structures

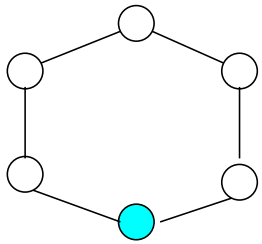
ISLAND MODEL



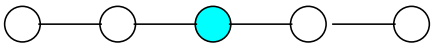
SPIDER MODEL



LOOP MODEL

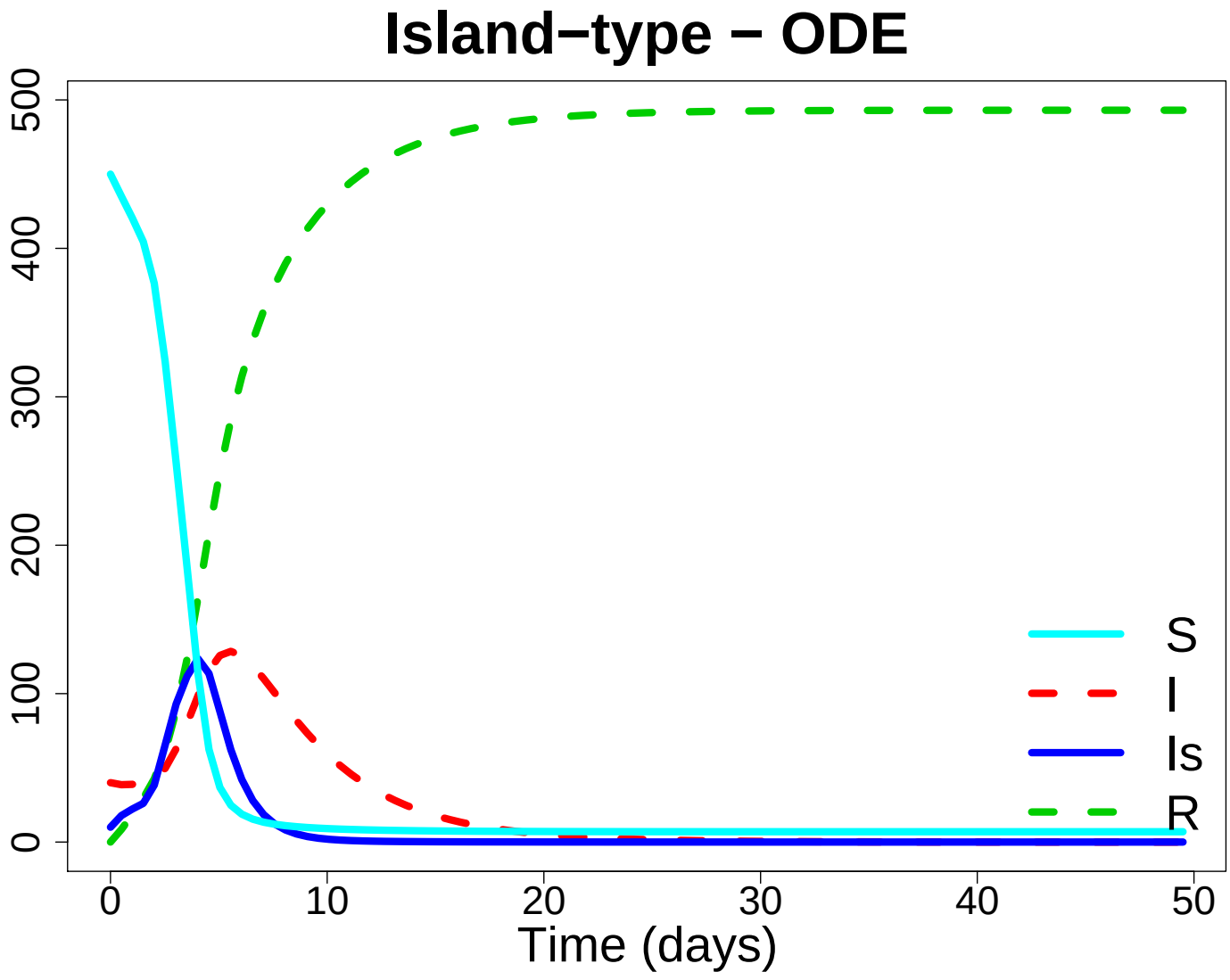


NECKLACE MODEL



The connections between the patches indicate how individuals might move between patches, thus relaying infections through the metapopulation.

Comparing structures



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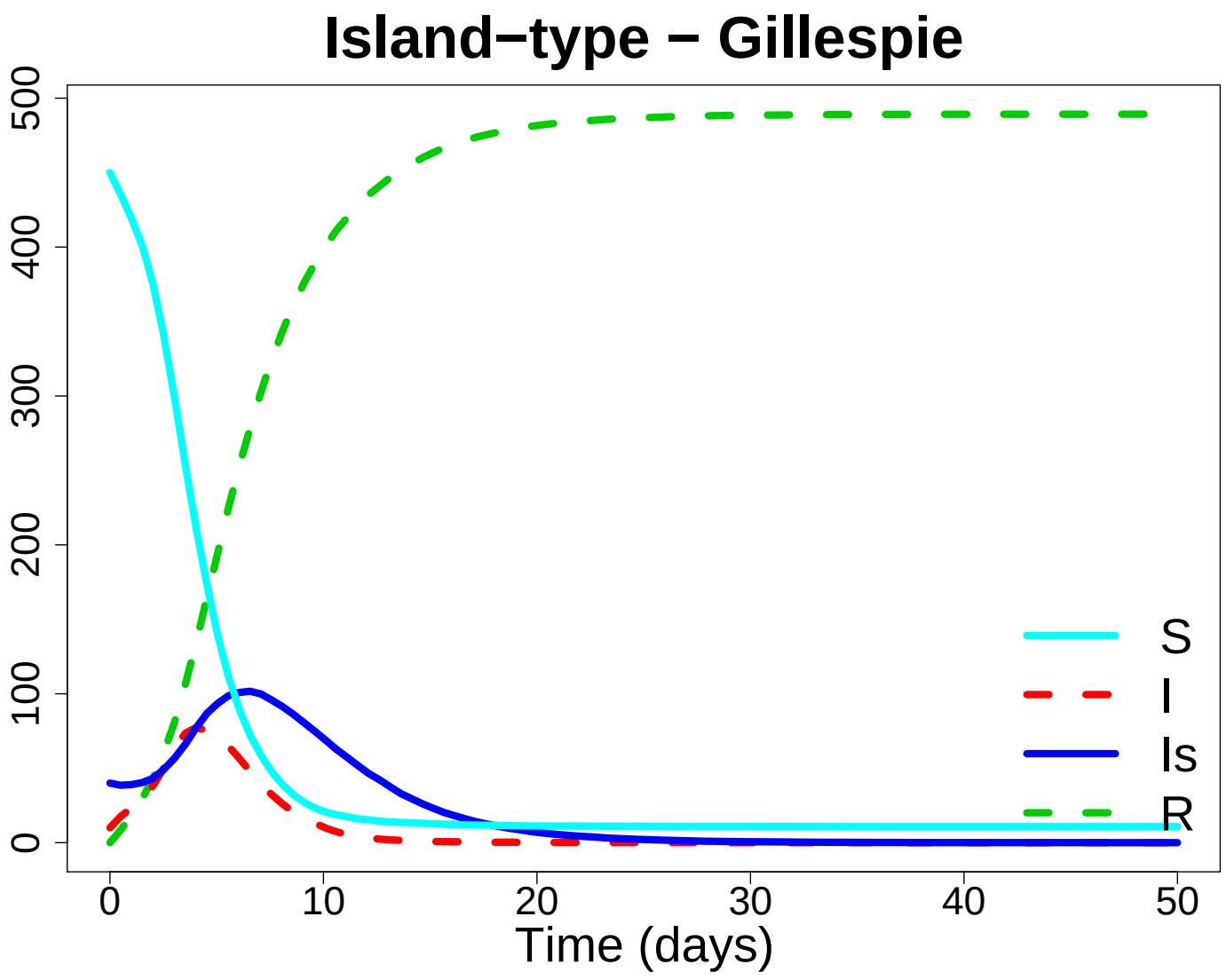

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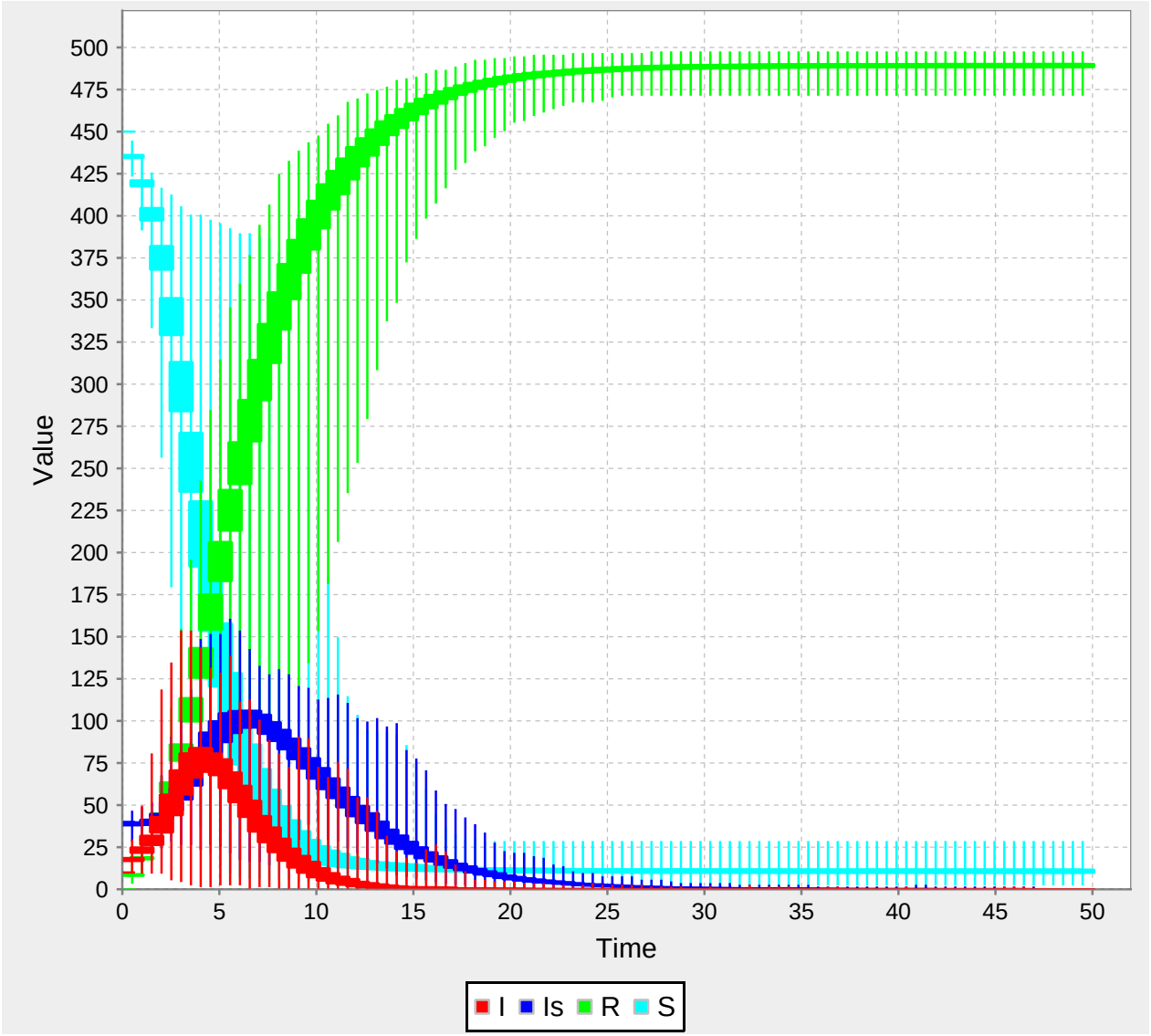

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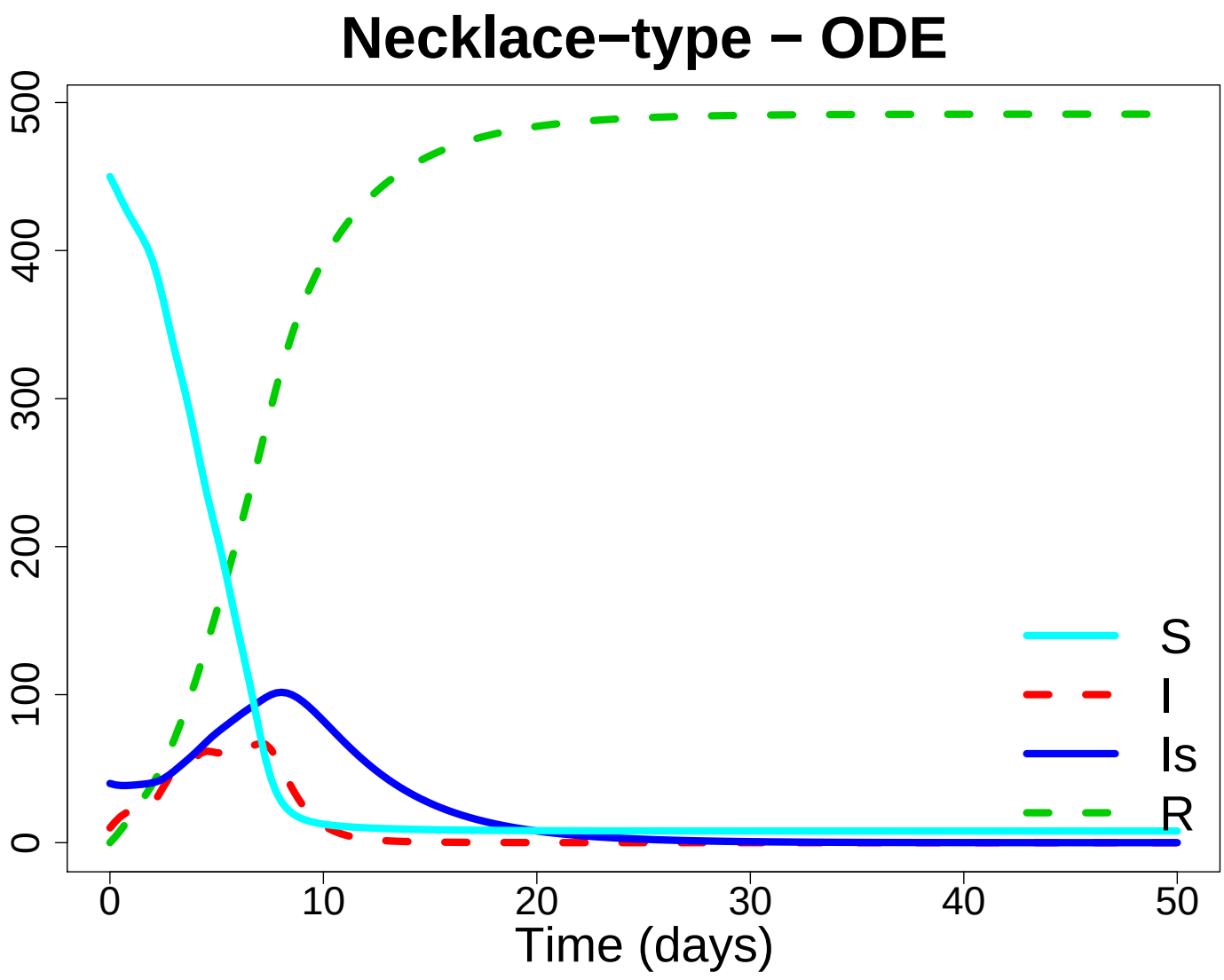

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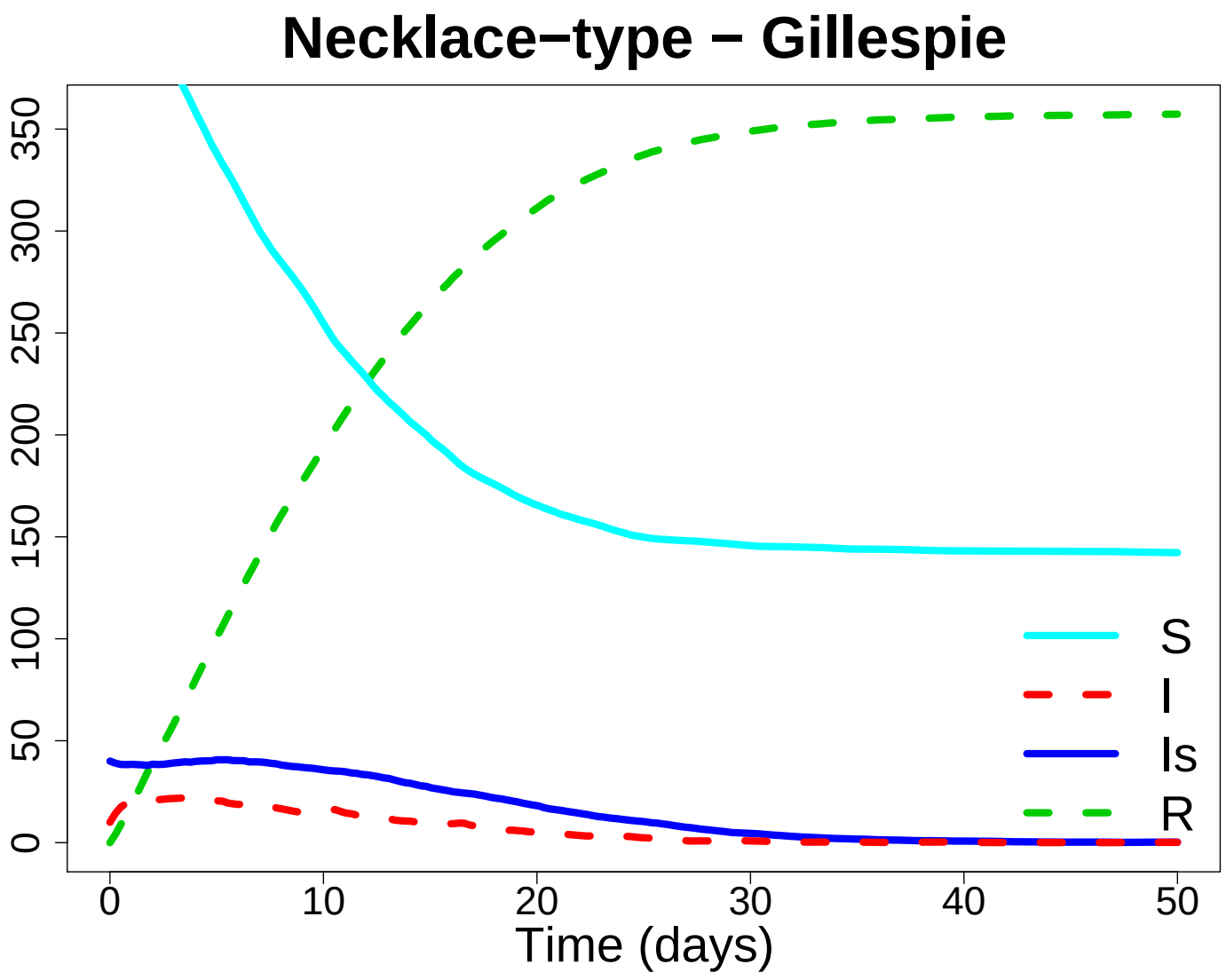

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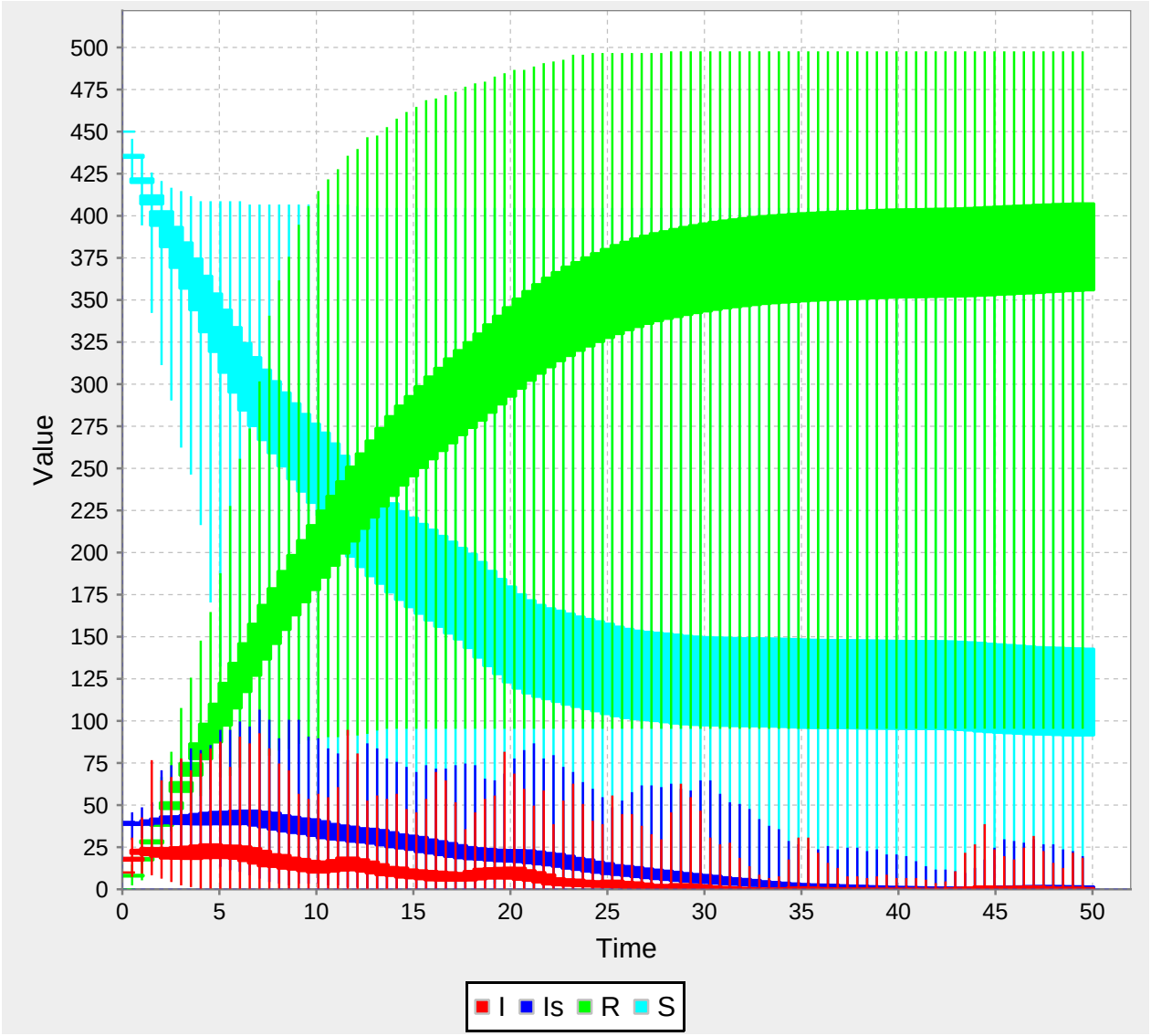
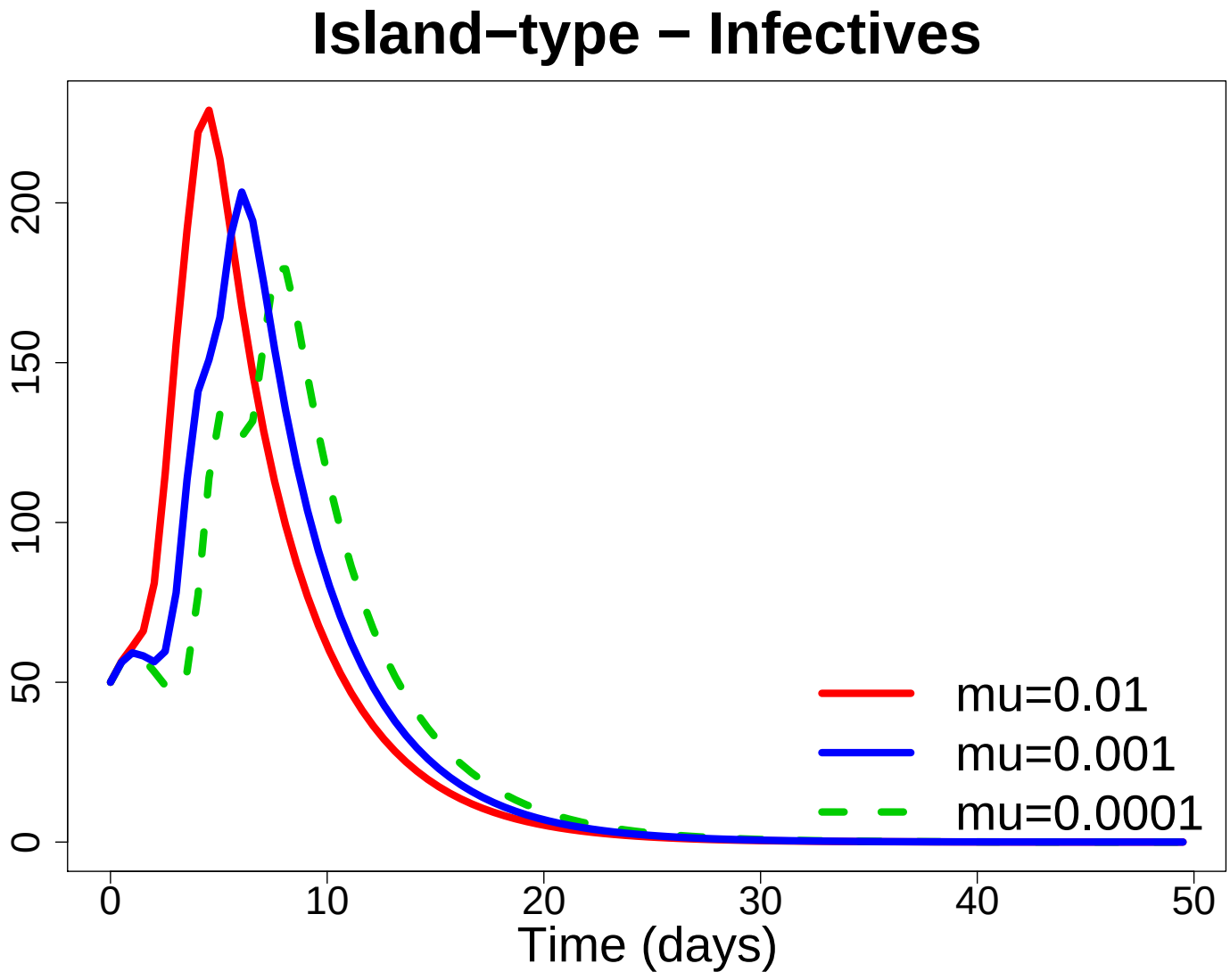


The effect of the migration rate



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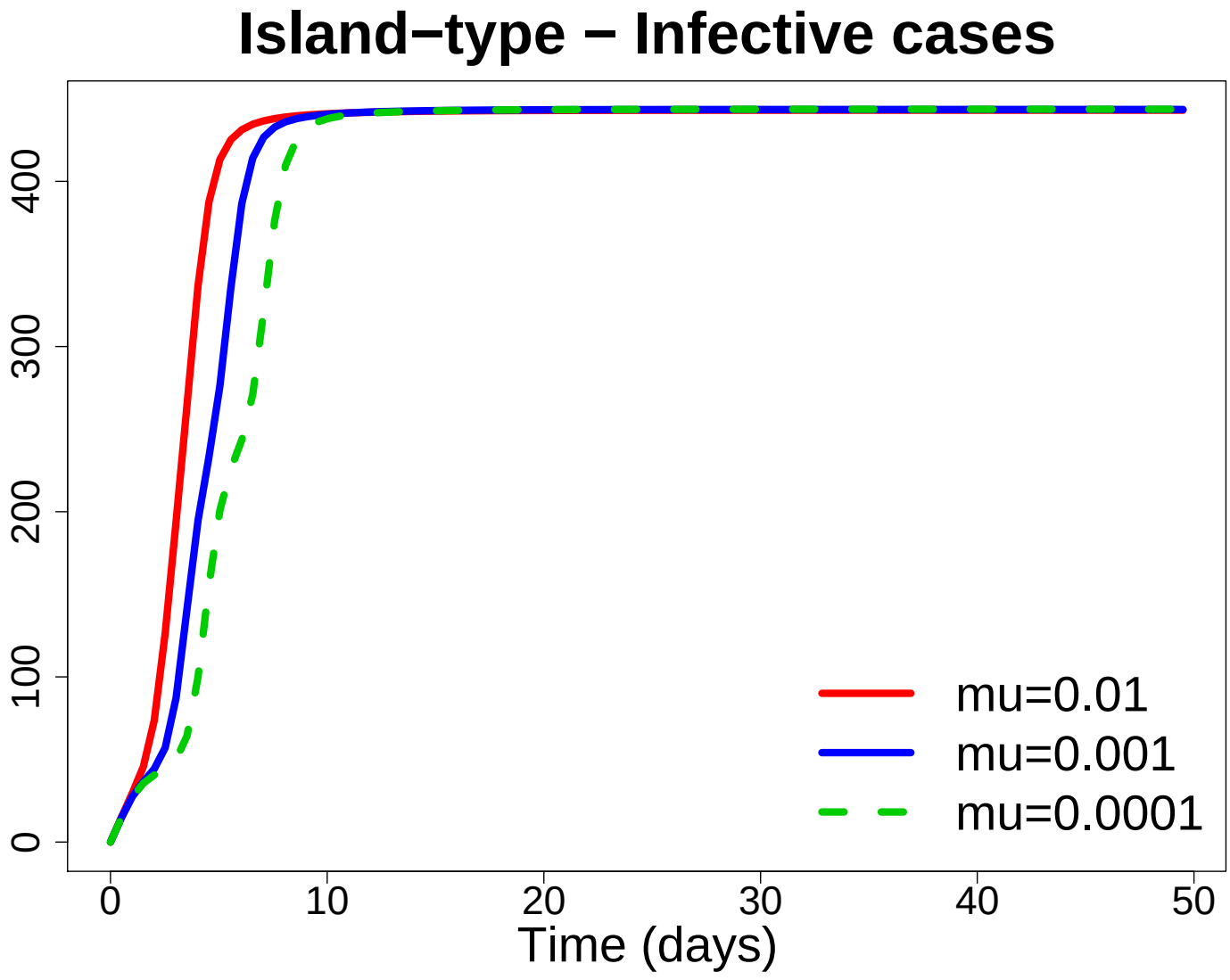

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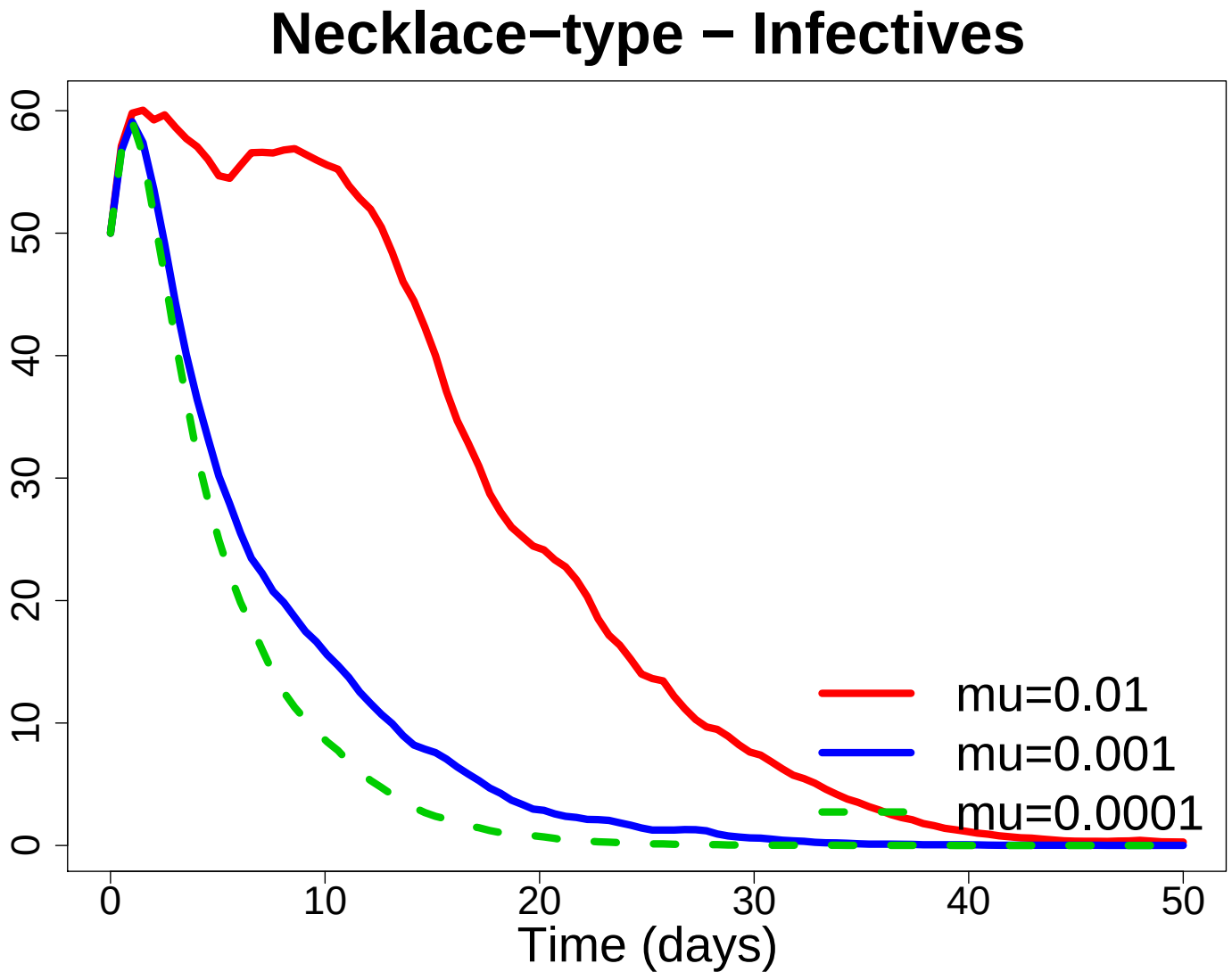

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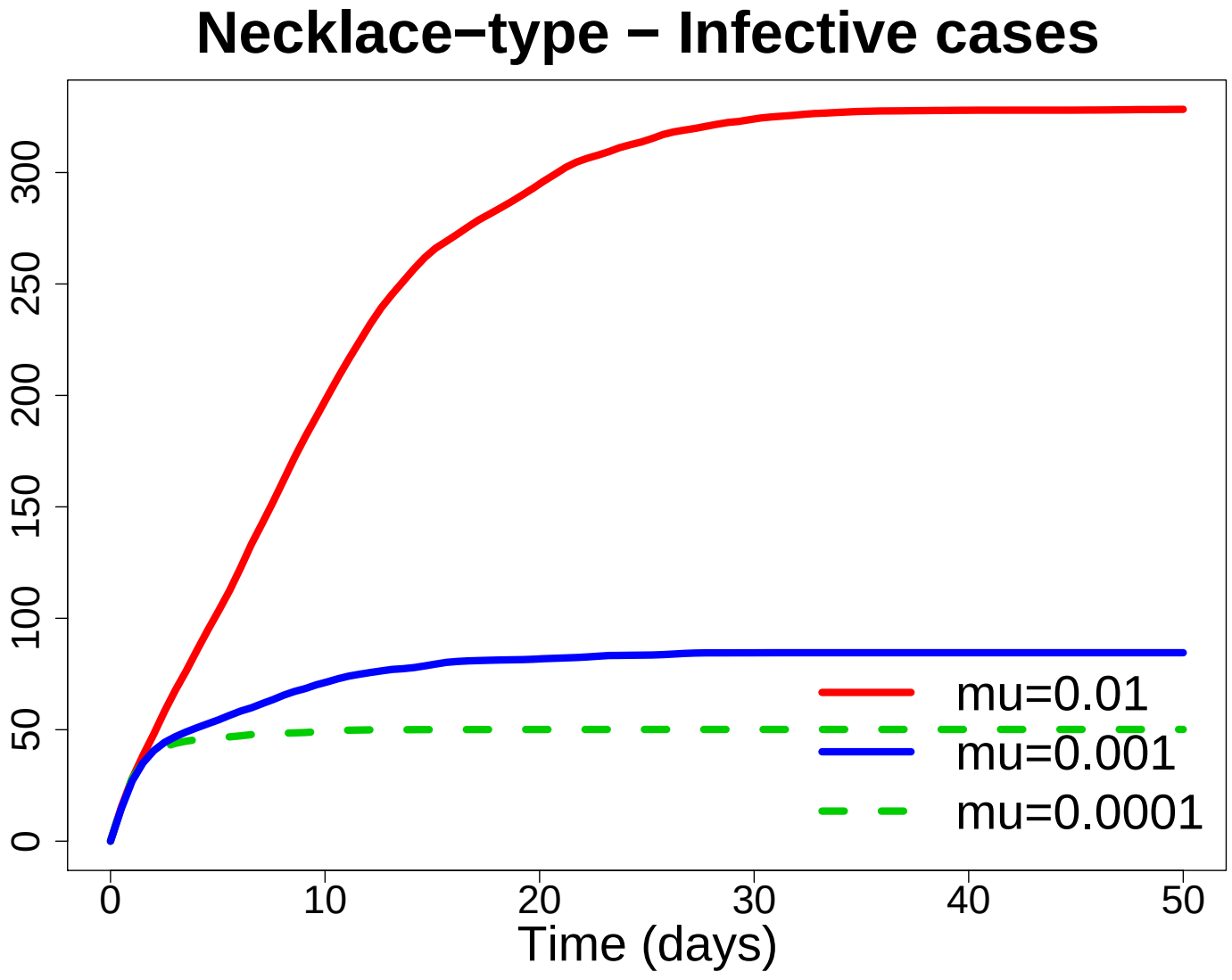

Multiple locations, treatment and drug resistance

In the paper the final model is used to study the effects of:

- multiple locations and the spatial arrangement of those locations
- giving treatment to all symptomatic individuals — there is some delay before treatment takes effect;
- some individuals are infected with a form of the virus which is resistant to treatment;
- One third of the susceptible and asymptomatic populations are given a prophylaxis which reduces the transmission rate by 70%.

All these features are easy to express in the Bio-PEPA model but it becomes rather verbose.

Conclusions

- Using a process algebra allows finer grain control of the forms of interaction between individuals than the standard approach based on fitting predefined ODEs.
- In some circumstances, particularly when locations are considered, stochastic simulations are appropriate forms of analysis because the populations of individual patches may become relatively small.
- Whilst developed for modelling biochemical pathways Bio-PEPA does seem capable of expressing a wide variety of epidemiological models.
- However, for models with more complex structure it might be appropriate to develop a more graphical user interface for model construction.