Quantitative Methods in Systems Biology
Part II: Modelling with Process Algebras

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SFM:08-Bio Summerschool
Bertinoro, Italy

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Acknowledgements

M. Calder, A. Duguid, S. Gilmore and J. Hillston,

Stronger computational modelling of signalling pathways using both continuous and discrete-state methods,

Computational Methods in Systems Biology,

Trento, Italy, 2006.

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The aim was not to make grand discoveries about this particular signalling pathway — more to explore the boundaries of modelling biological systems with PEPA.

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HIDING:	P/L	abstraction $\alpha \in L \Rightarrow \alpha \rightarrow \tau$

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In the PEPA modelling we have been doing we have experimented with more abstract mappings between process algebra constructs and elements of signalling pathways.

For example, we focus on species (c.f. a type rather than an instance, or a class rather than an object) and use local states to capture discretized levels of concentration.

Reagent-centric modelling

Role	*Impact on reagent*	*Impact on reaction rate*
Producer	decreases concentration	has a positive impact, i.e. proportional to current concentration
Product	increases concentration	has no impact on the rate, except at saturation
Enzyme	concentration unchanged	has a positive impact, i.e. proportional to current concentration
Inhibitor	concentration unchanged	has a negative impact, i.e. inversely proportional to current concentration

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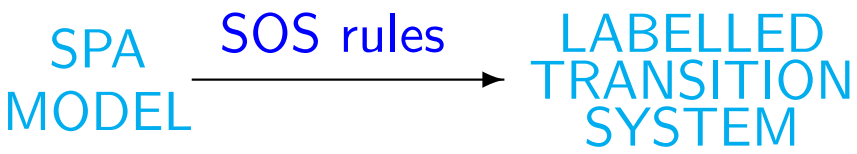

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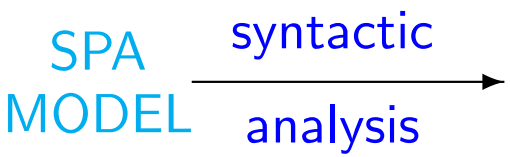

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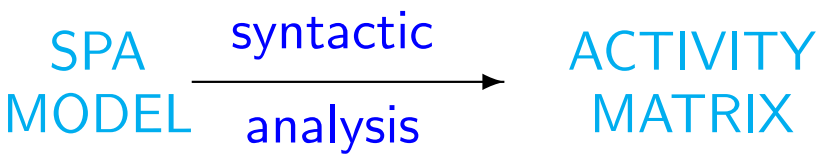

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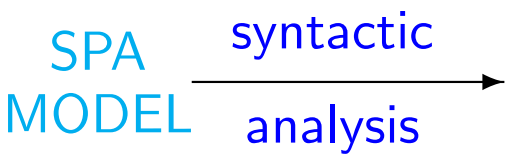

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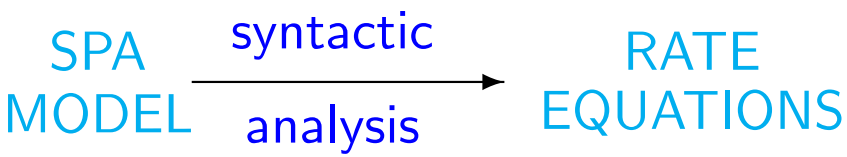

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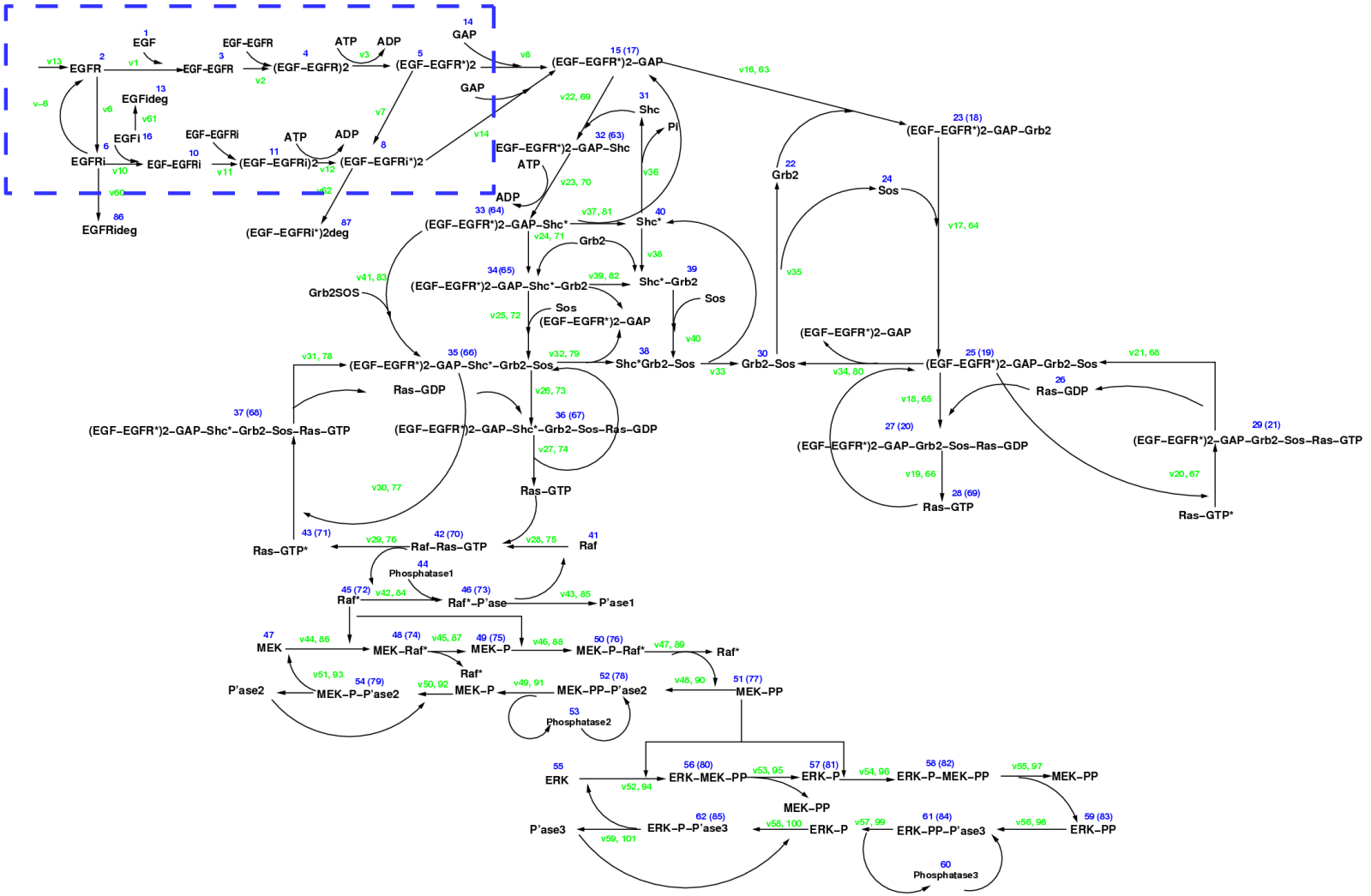
Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

Outline

Schoeberl *et al.*'s model of the MAP Kinase Cascade

- Published in *Nature Biotechnology* 20:370-375 in 2002.
- Influential, cited by more than 150 subsequent published papers.
- Consists of 94 reagent species involved in 125 reactions.
- Substantial ODE model consisting of 94 state variables and 95 parameters.
- PEPA model constructed "by hand", with help of a graphical representation.
- Analysis performed by numerical ODE integrators of the Matlab numerical computing platform.

The MAP Kinase Cascade



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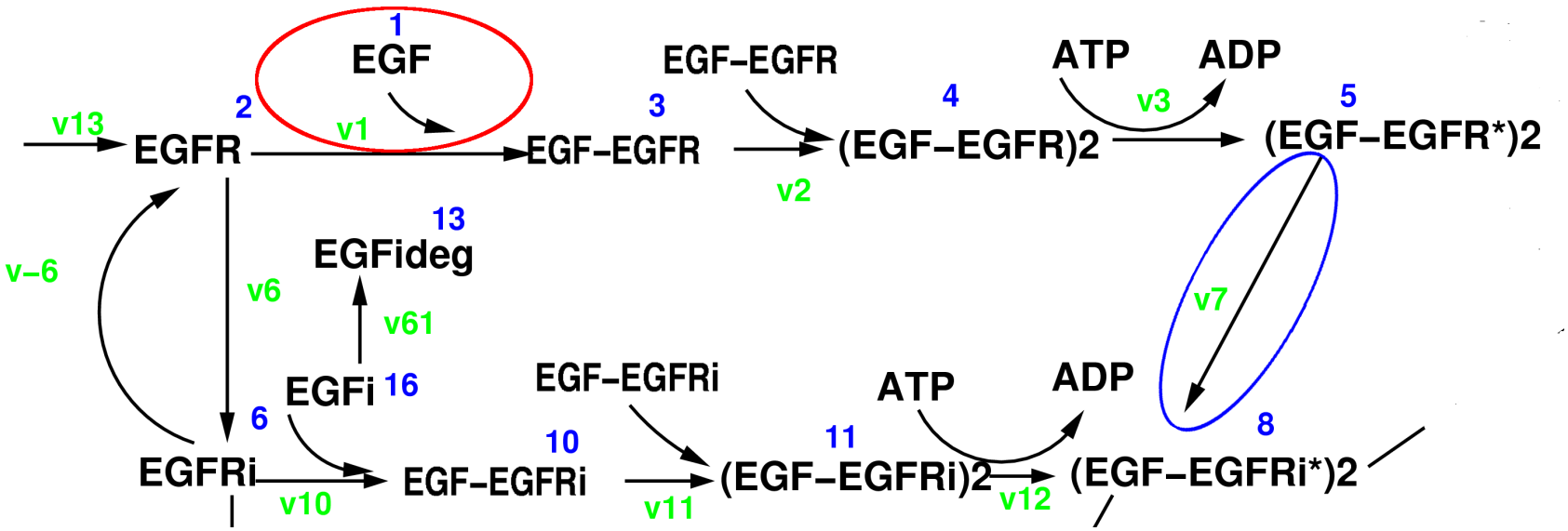

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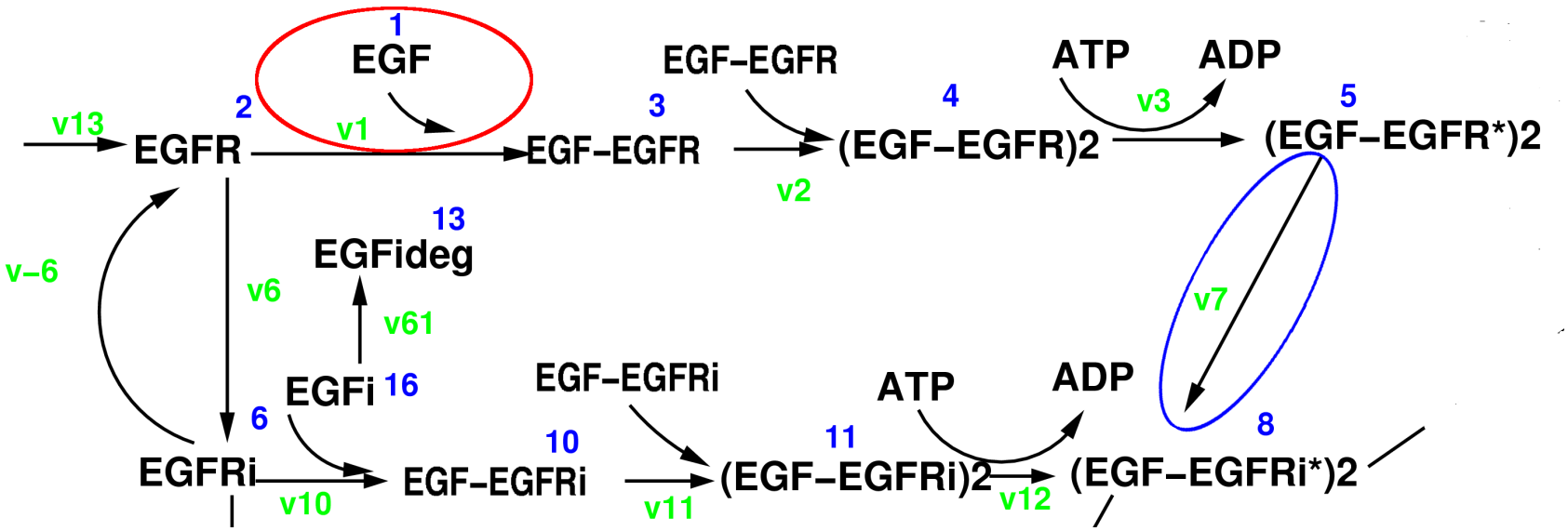

There are many ambiguities in the graphical representation, e.g.

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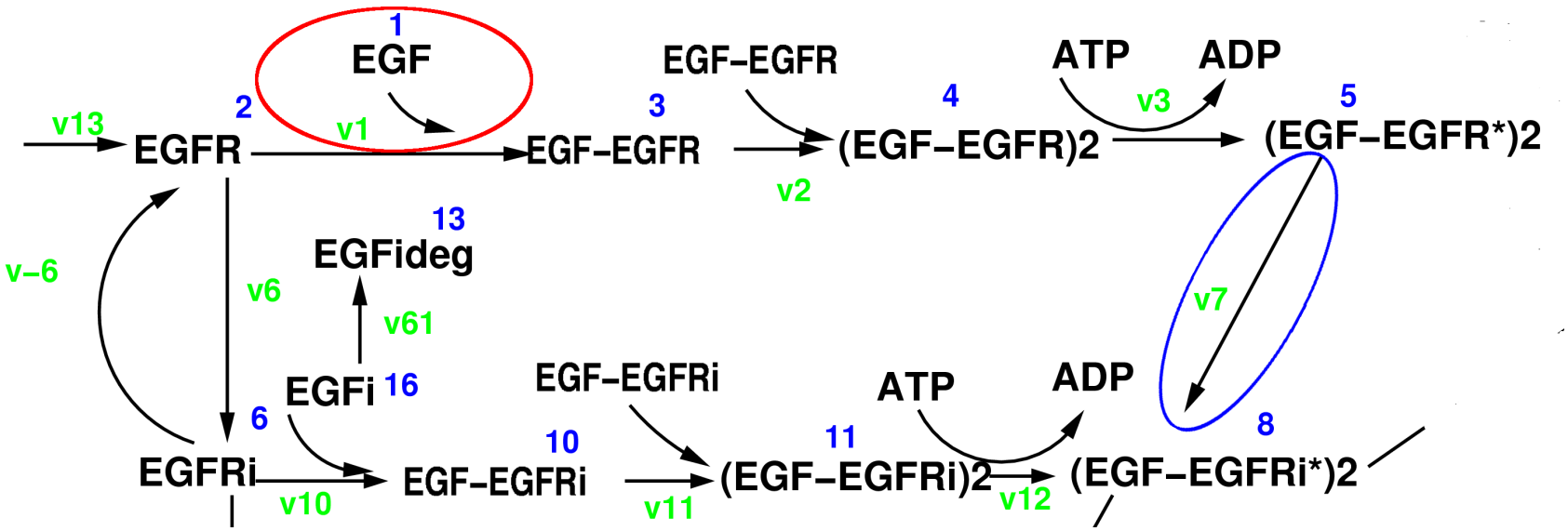

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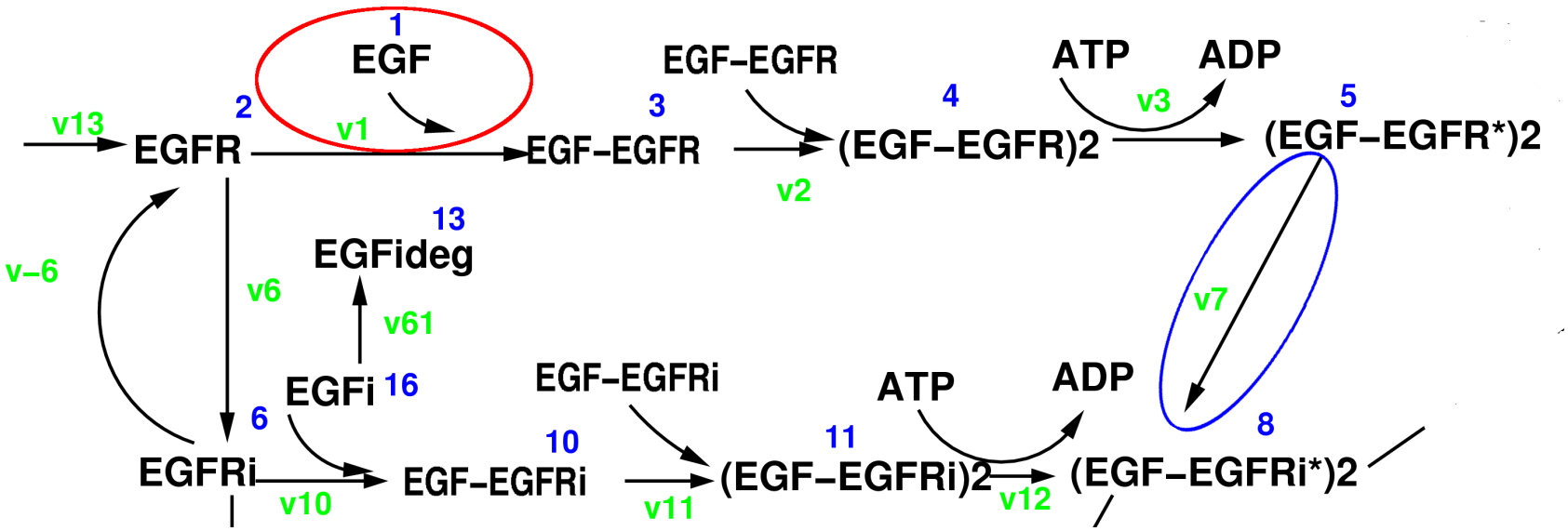

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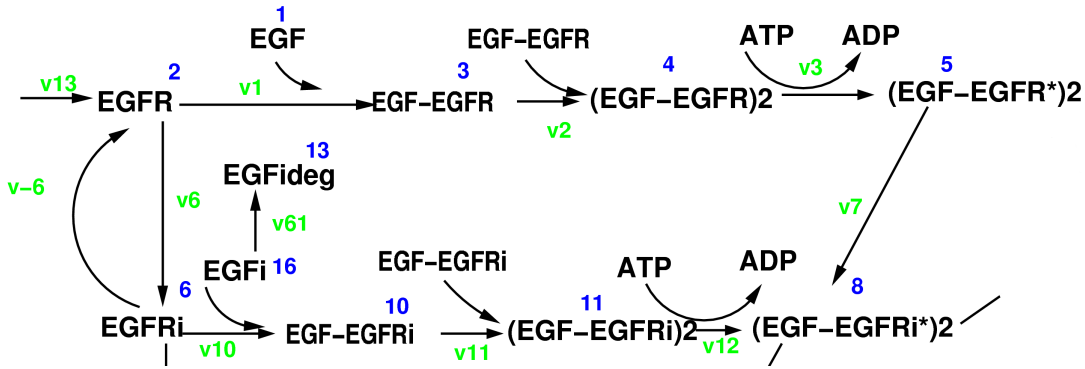
- An infinite supply of EGF is assumed;
- Reaction *v7* is uni-directional whereas all others are reversible.

Extracts from the MAP Kinase PEPA model



$$\mathrm{EGF_H} \stackrel{def}{=} (v_1, k_1).\mathrm{EGF_H}$$

$$\mathrm{EGFR_H} \stackrel{def}{=} (v_1, k_1).\mathrm{EGFR_L} + (v_6, k_6).\mathrm{EGFR_L}$$

$$\mathrm{EGFR_L} \stackrel{def}{=} (v_{\text{-}1},\ k_{\text{-}1}).\mathrm{EGFR_H} + (v_{\text{-}6},\ k_{\text{-}6}).\mathrm{EGFR_H} + (v_{13}, k_{13}).\mathrm{EGFR_H}$$

$$\text{EGF-EGFR}_\mathrm{H} \stackrel{def}{=} (v_2, k_2).\text{EGF-EGFR}_\mathrm{L} + (v_{\text{-}1}, k_{\text{-}1}).\text{EGF-EGFR}_\mathrm{L}$$

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The PEPA model

Similar PEPA definitions were constructed for each of the 94 species in the pathway.

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In order to complete the model we also needed to capture the interactions (i.e. cooperations) between the reagents. In this case we assumed that whenever reagents participated in reactions with the same name they did so in cooperation. The system equation was then automatically generated.

Validation of the PEPA model

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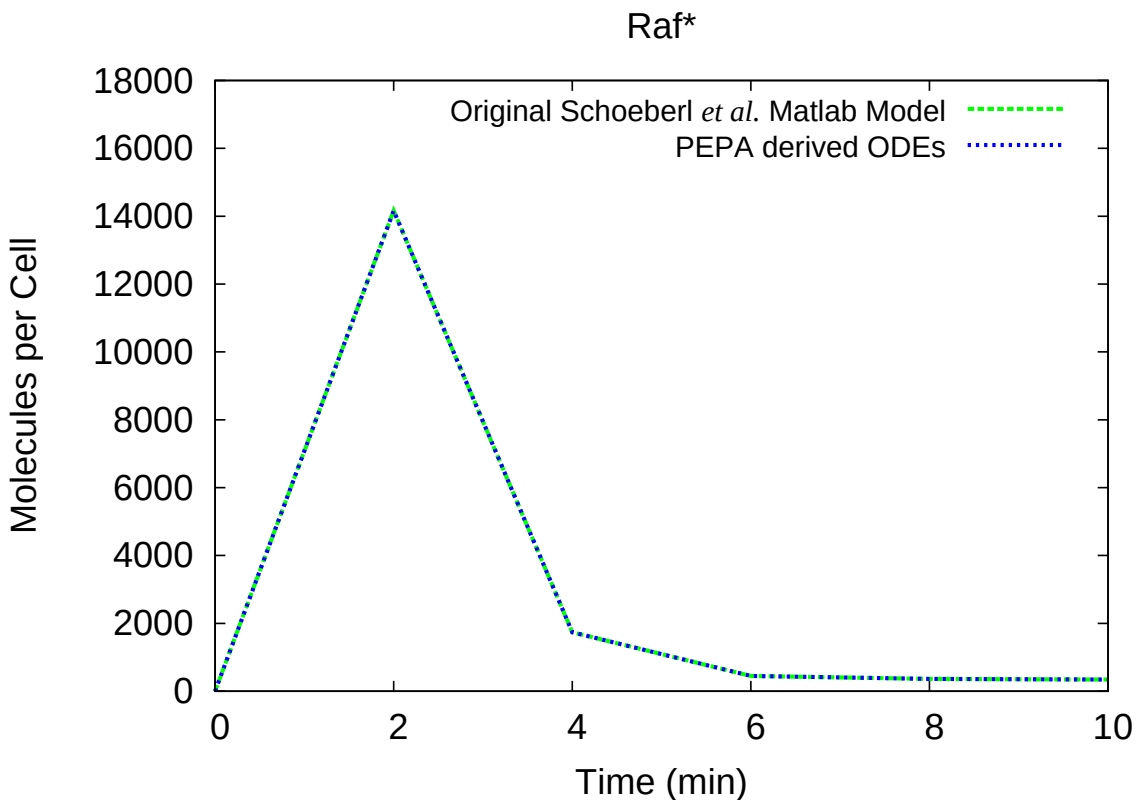
- In the first instance we derived a set of ODEs in a format suitable for Matlab.
- These could not be compared directly with Schoeberl *et al*'s ODEs due to different representations being used, but we compared them empirically in terms of the results.

Comparing Original Results and PEPA Derived ODEs



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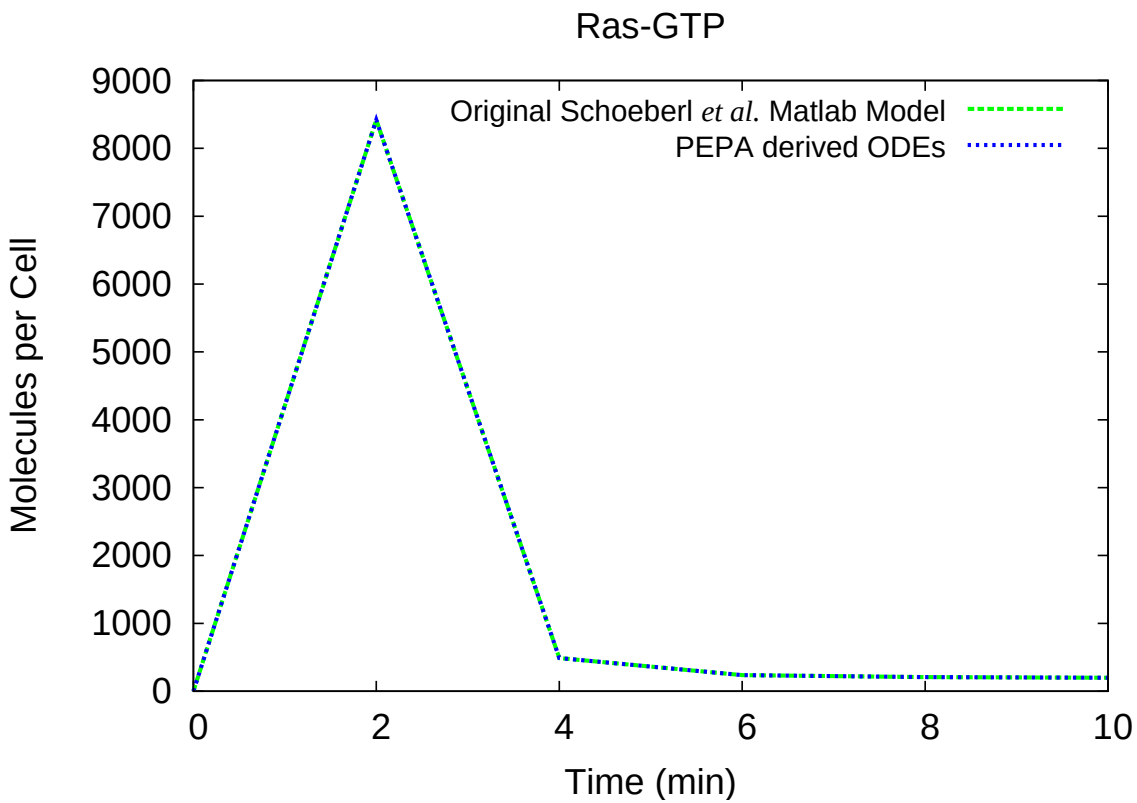
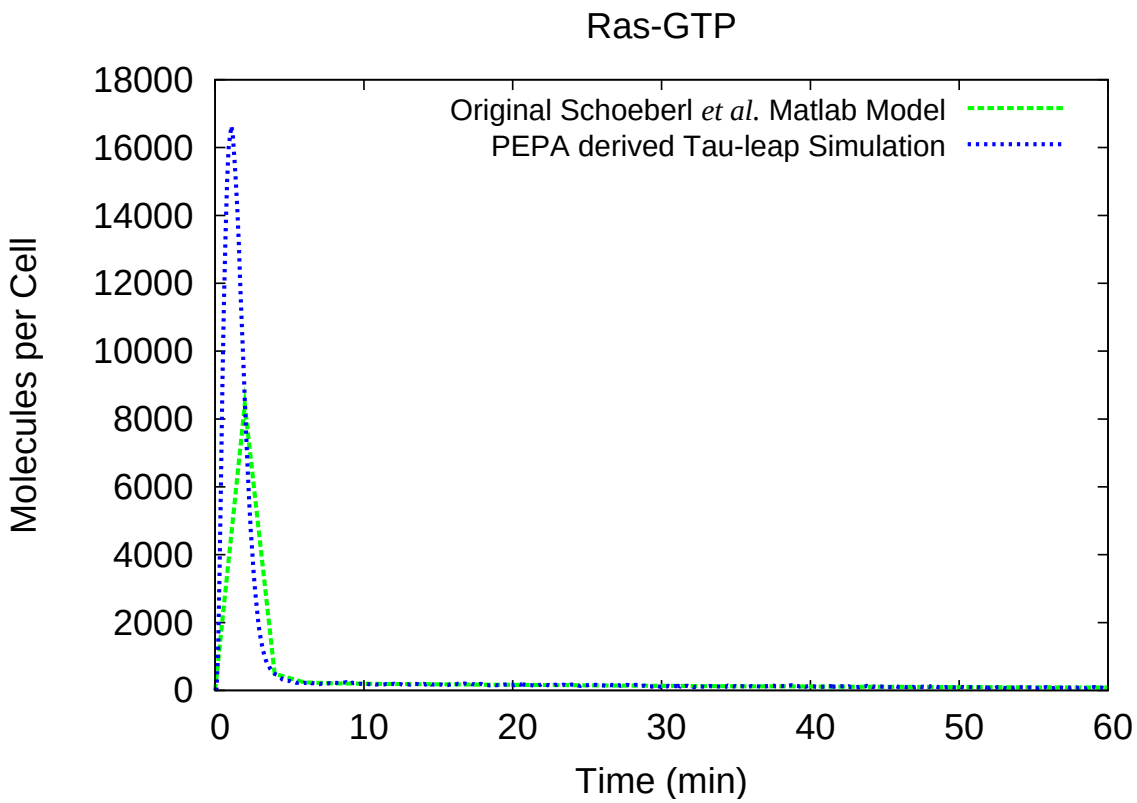


The PEPA derived ODEs return the same results as the Schoeberl *et al.* Matlab model.

Validation of the PEPA model

- We used an alternative mapping from the PEPA to generate a stochastic simulation of the system, and compared our stochastic simulation with the published ODE results.

Original Results and PEPA Derived Tau-leap Simulation



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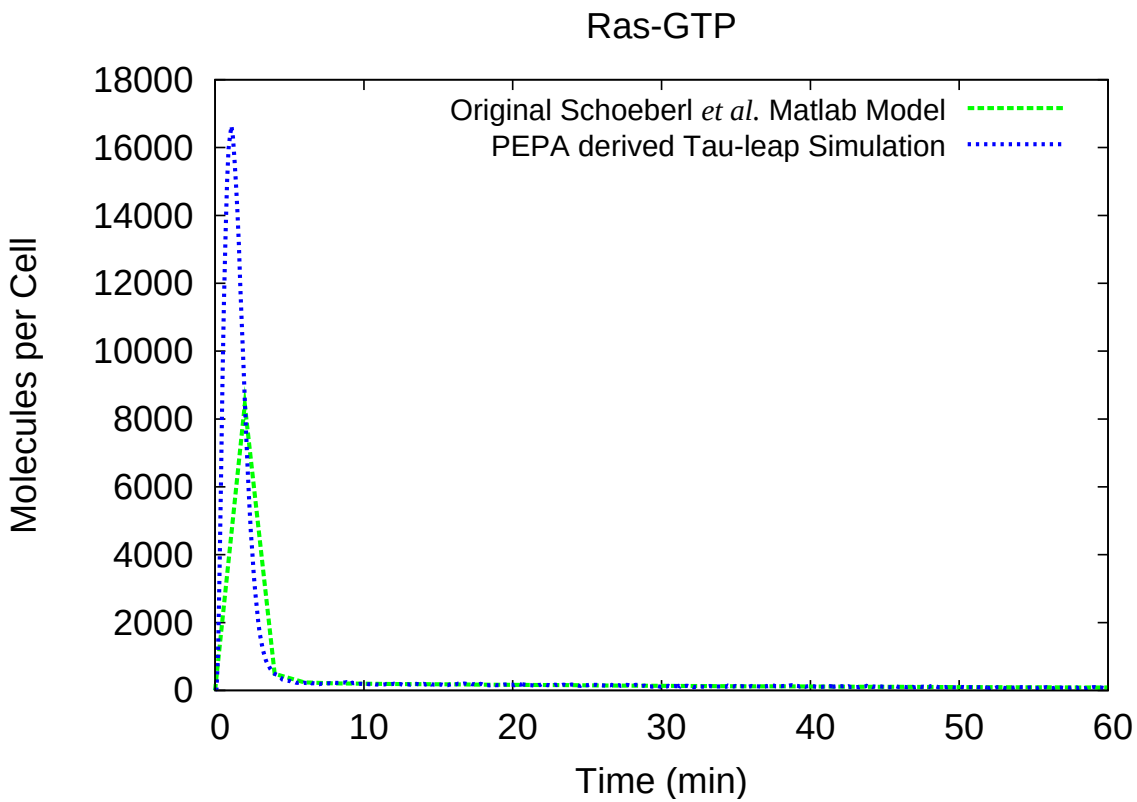

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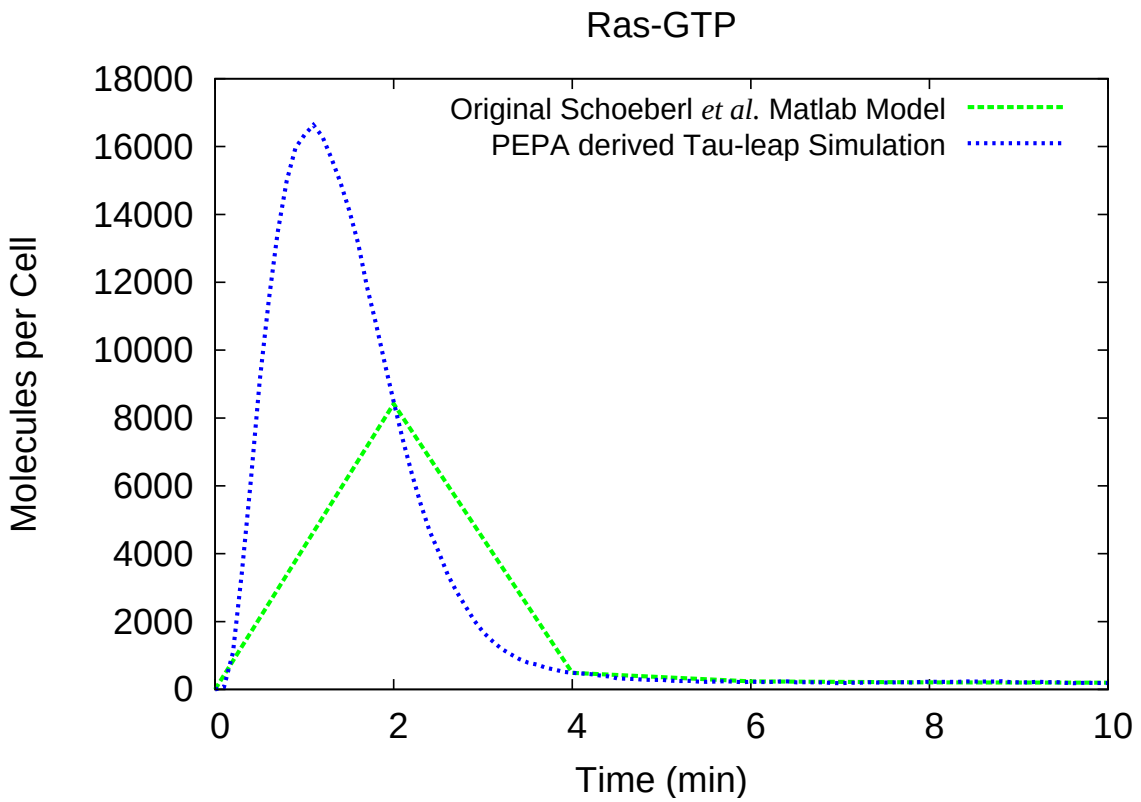

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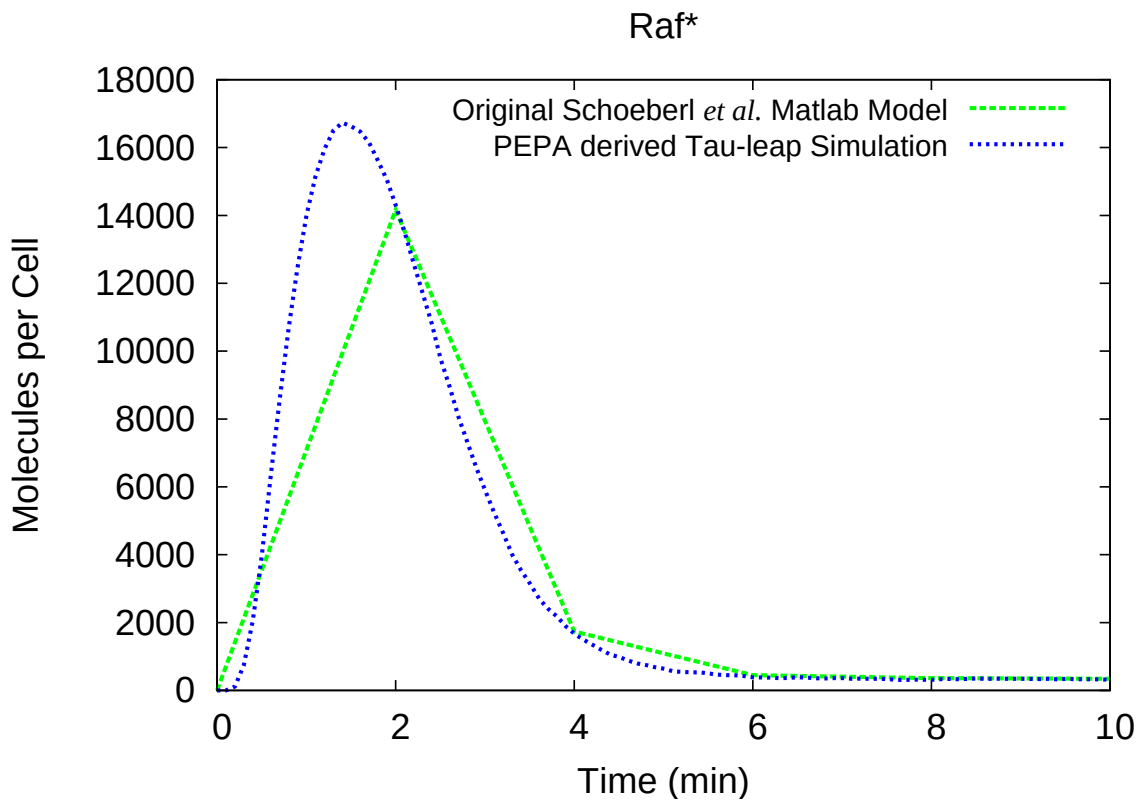

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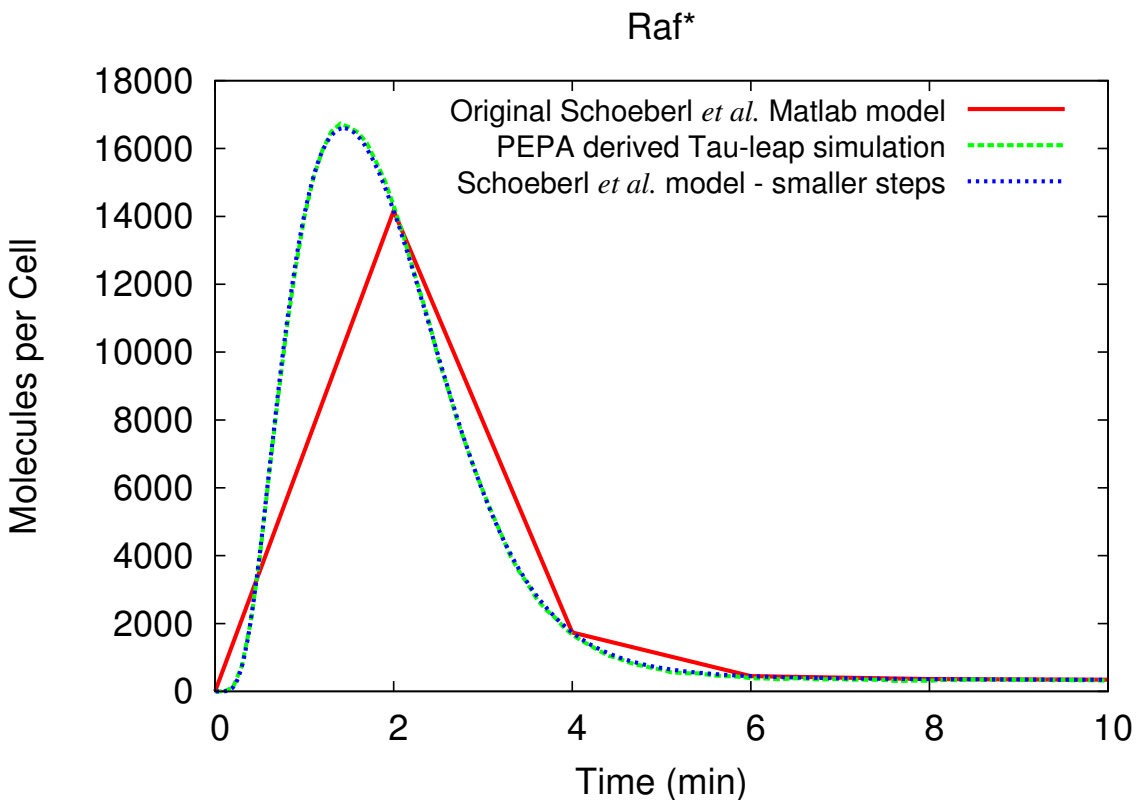
Corrected Time Step in Matlab Model



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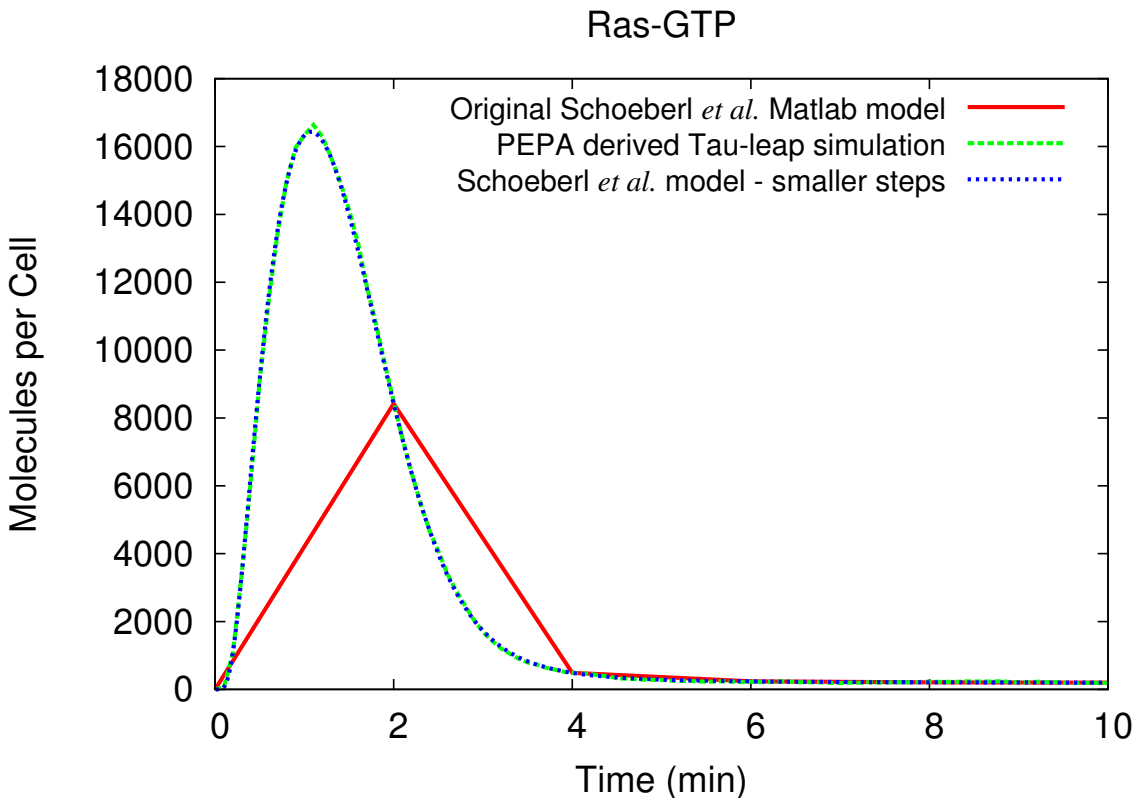

The original parameters for the Matlab model stepped over the true peak. The Tau-leap simulation was in fact returning the correct results.

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- It has been shown that PEPA can cope with models of this size.
- PEPA offers a cleaner, more precise view of the system.
- Moreover, PEPA allows multiple forms of analysis.
- This ability led to the discovery that the true peaks of Raf* and Ras-GTP concentrations were incorrectly calculated in the original analysis.