Spatio-temporal Biological Process Modelling

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Outline

Process algebras

- history
  - developed to model concurrent computing (mid 1980's)
  - originally no notion of time or space, some extensions
  - Hillston developed PEPA, stochastic process algebra (1996)
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  - Hillston developed PEPA, stochastic process algebra (1996)
  - Hillston developed ODE interpretation of PEPA (2005)
- Bio-PEPA, a biological process algebra
  - close match between modelling artificial and natural systems
  - developed by Ciocchetta and Hillston (2009)
  - extension of PEPA, functional rates and stoichiometry

Process algebras (cont)

- what is a process algebra?
  - compact and elegant formal language
  - behavior given by semantics defined mathematically
  - classical process algebras: labelled transition systems
  - stochastic process algebras: continuous time Markov chains

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  - classical process algebras: labelled transition systems
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- why use Bio-PEPA?
  - formalism to describe species and interactions
  - unambiguous, precise
  - different analyses available from a single description
    deterministic simulation (population view),
    stochastic simulation (individual view),
    continuous time Markov chain with levels (abstract view)

Bio-PEPA (in brief)

- species: reactions, stoichiometry, locations

$$S@L \stackrel{def}{=} (\alpha_1, \kappa_1)\ \mathtt{op}_1\ S@L\ +\ \ldots\ +\ (\alpha_n, \kappa_n)\ \mathtt{op}_n\ S@L$$

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  - $\mathcal{N}$ species quantities, minimums, maximums, step size
  - $\mathcal{K}$ parameter definitions
  - $\mathcal{F}$ functional rates for reactions, definition of f_α

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- definition of behavioural semantics

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- software tool for Bio-PEPA modelling

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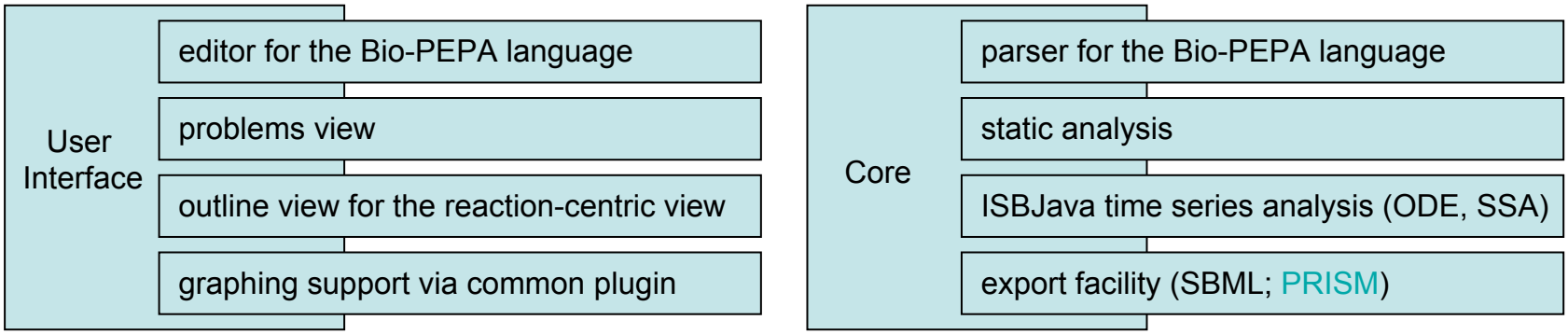

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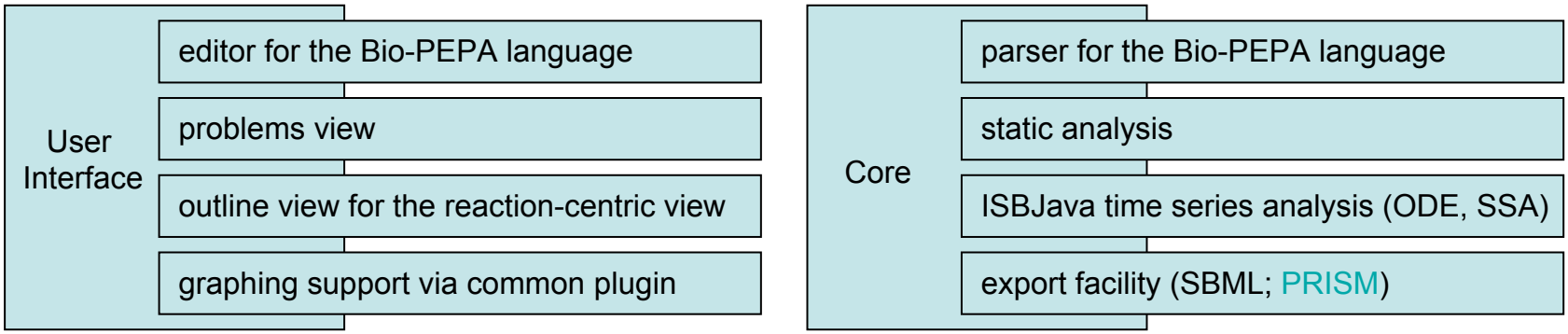
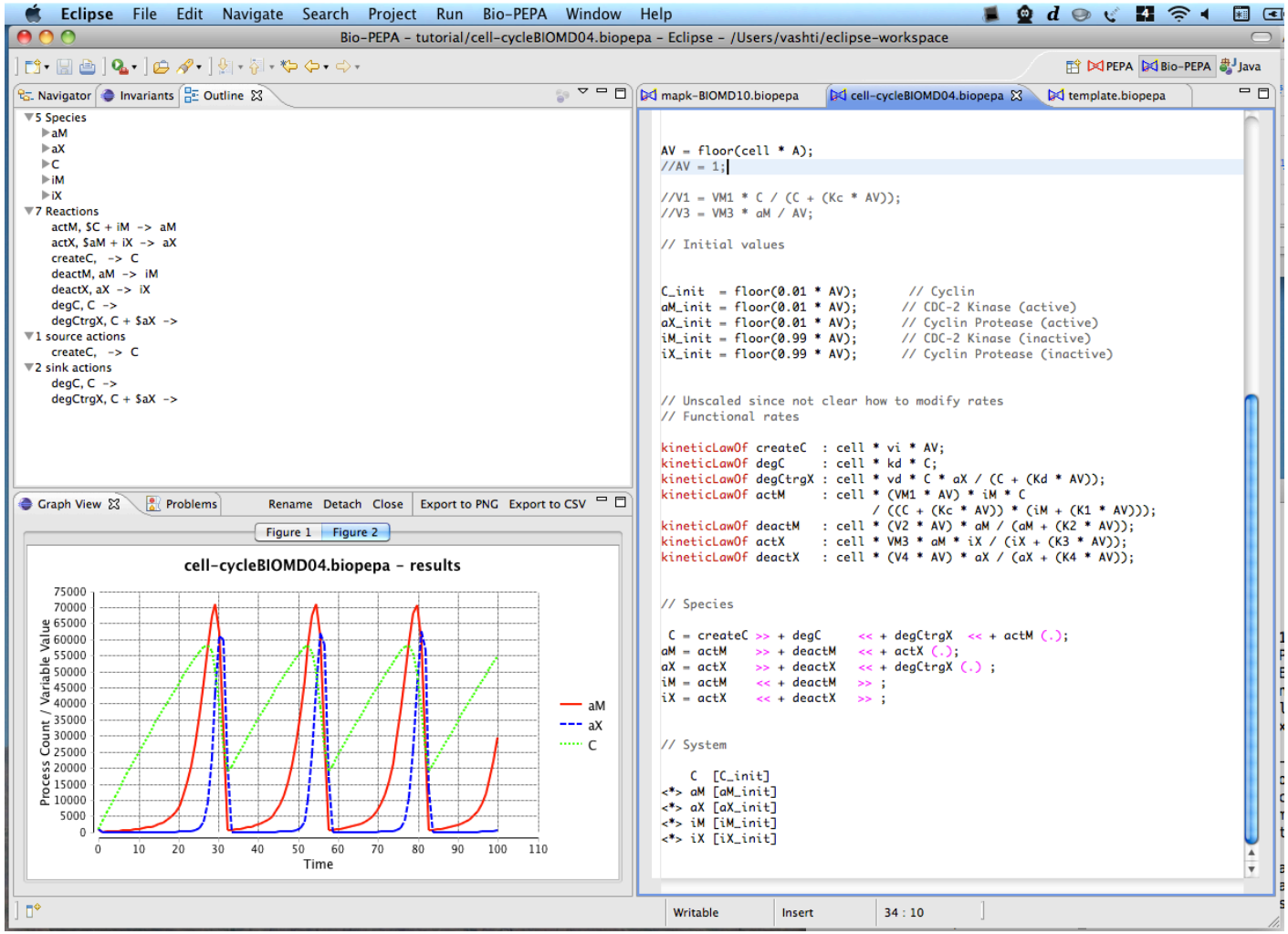


- available for download at `www.biopepa.org`
- case studies, publications, manuals

Bio-PEPA Eclipse Plug-in (cont)



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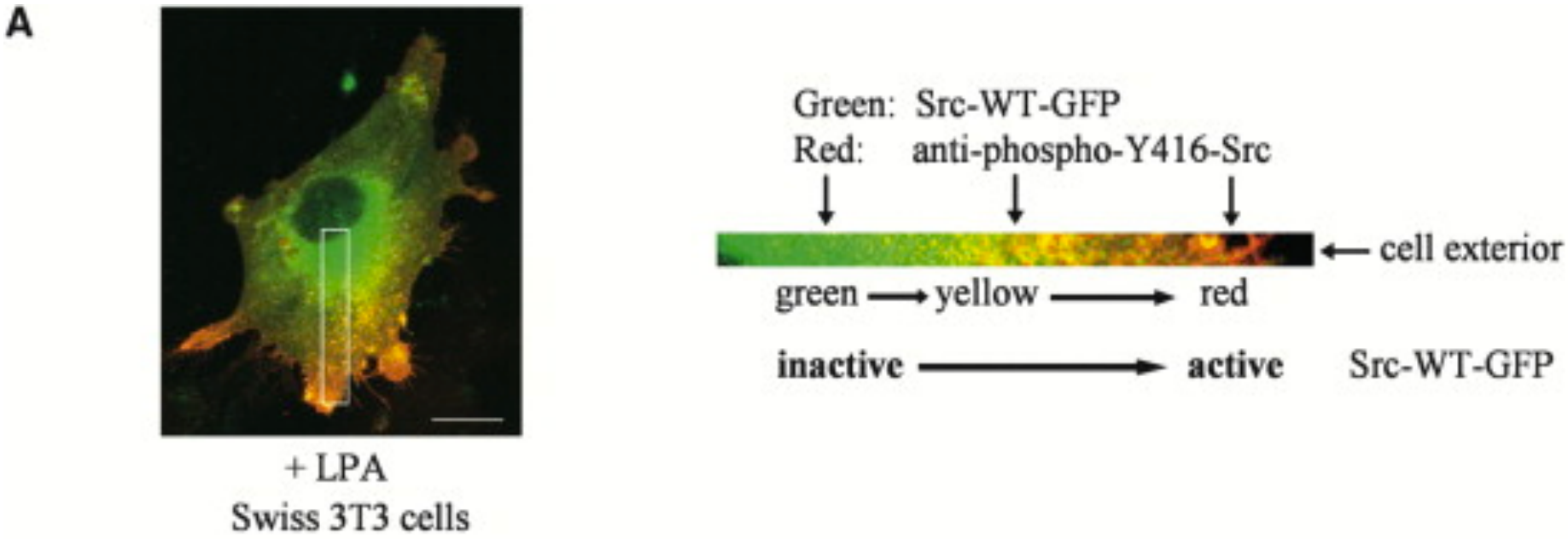
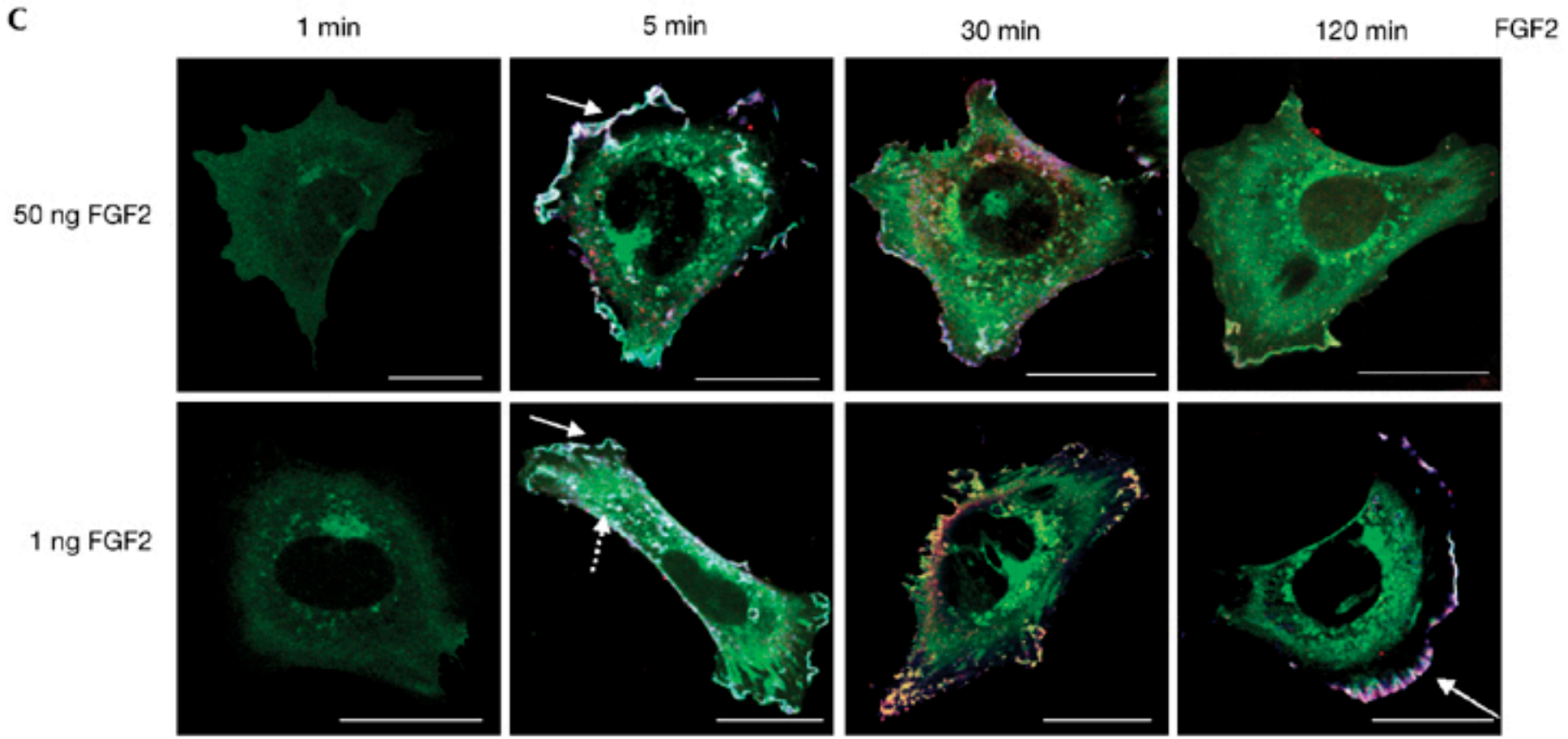
The persistence of active Src at the membrane is inversely related to the quantity of FGF added. (Sandilands *et al*, 2007)

Src: gradient from inactive to active



(Sandilands *et al*, Dev. Cell 7, 2004)

Src: persistence of response to FGF



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- identification of recycling loops: number and type
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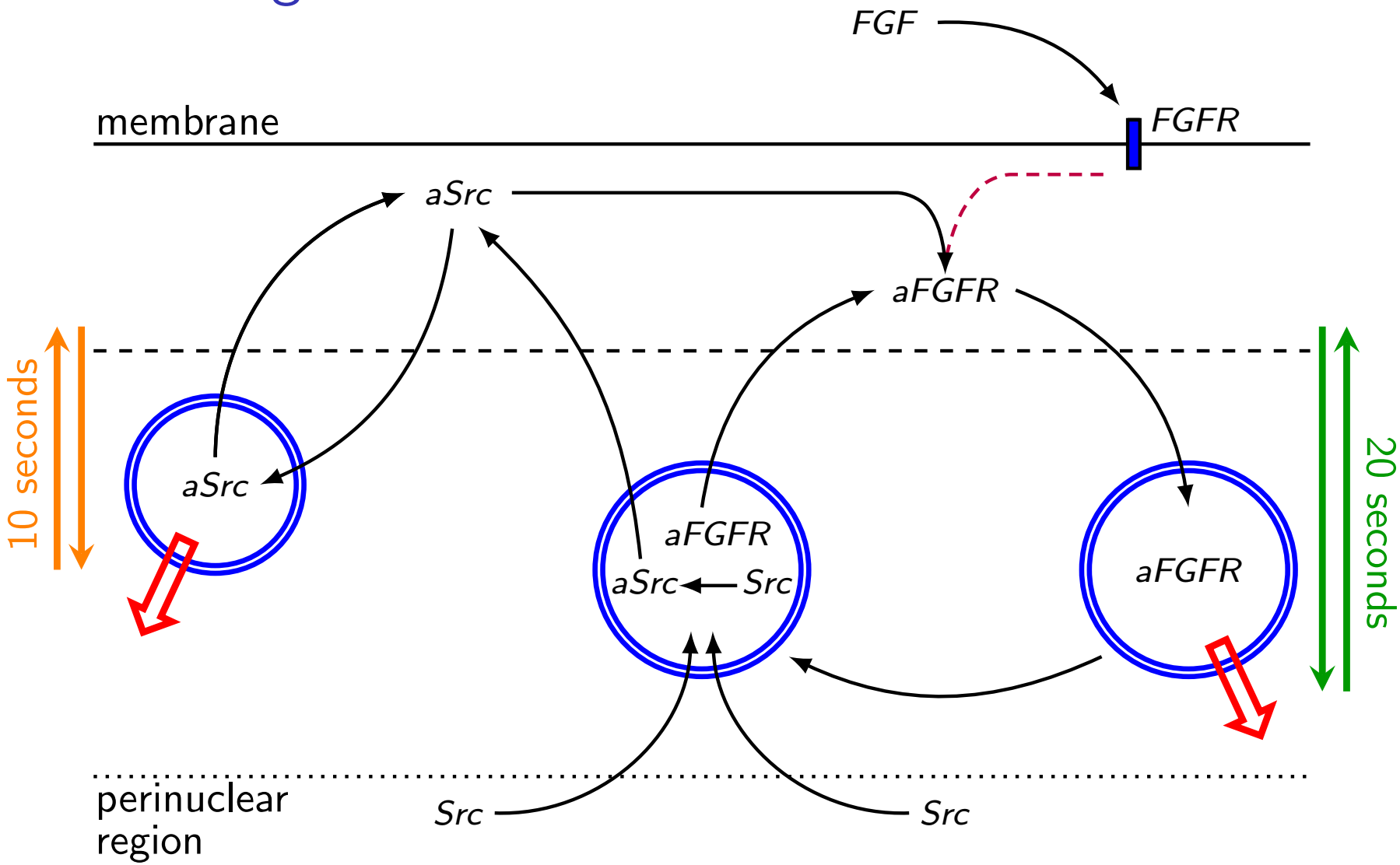
- qualitative
  - gradient of inactive versus active, activation within endosomes
  - endosome movement is directional along microfilaments/microtubules
- quantitative
  - estimates of endosome speeds and length of recycling loops
  - timing from FGF stimulation experiment

Src trafficking



Simplified Bio-PEPA model

- active Src at membrane

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              (in_sh,75) >> aSrc@mb + (in_long,100) >> aSrc@mb;
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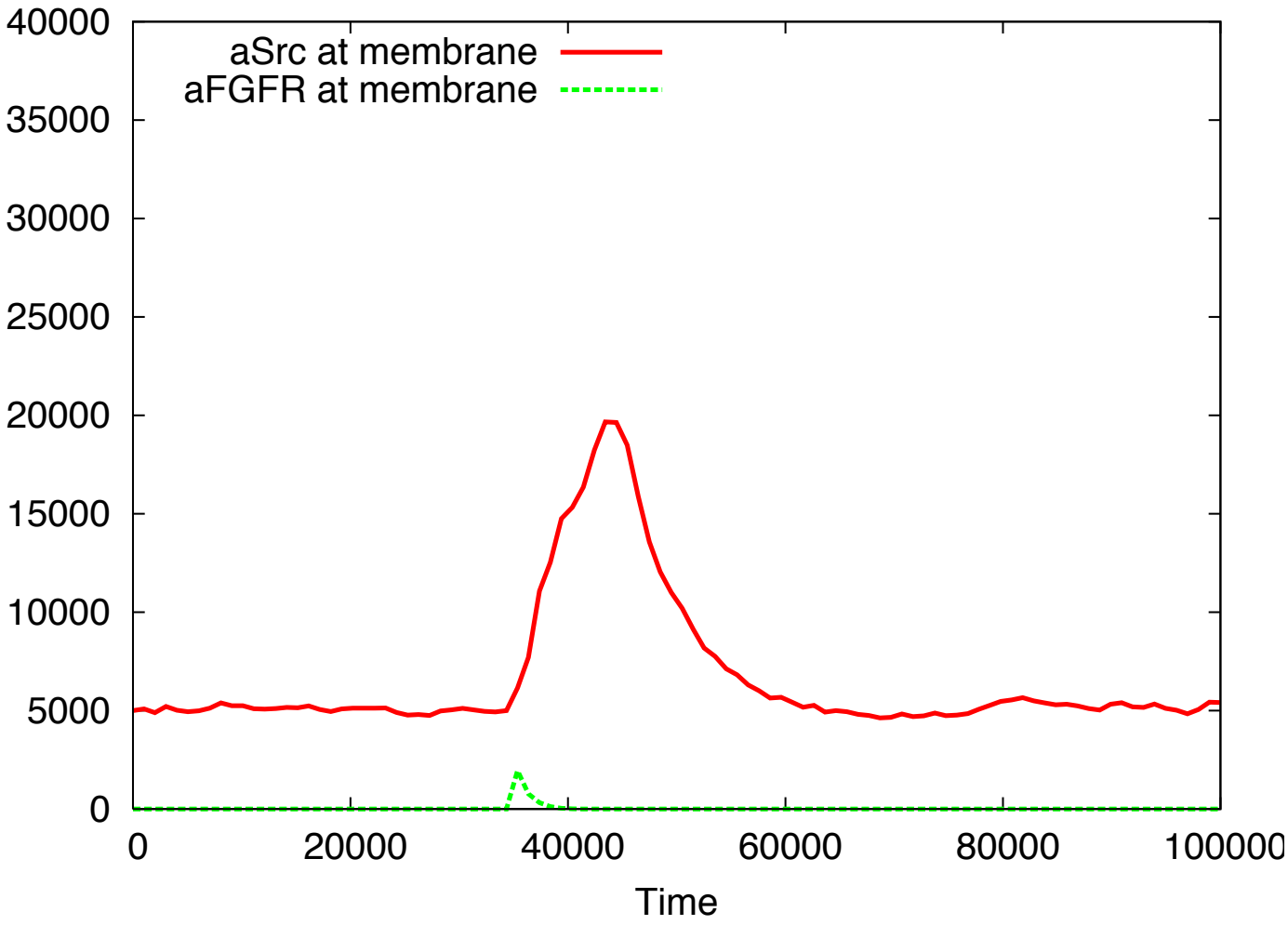
- reactions

```
out_sh:     150 aSrc   ->   Endo_short
 in_sh:   Endo_short   ->   75 aSrc
```

Two loop trafficking model – results



Circadian clock

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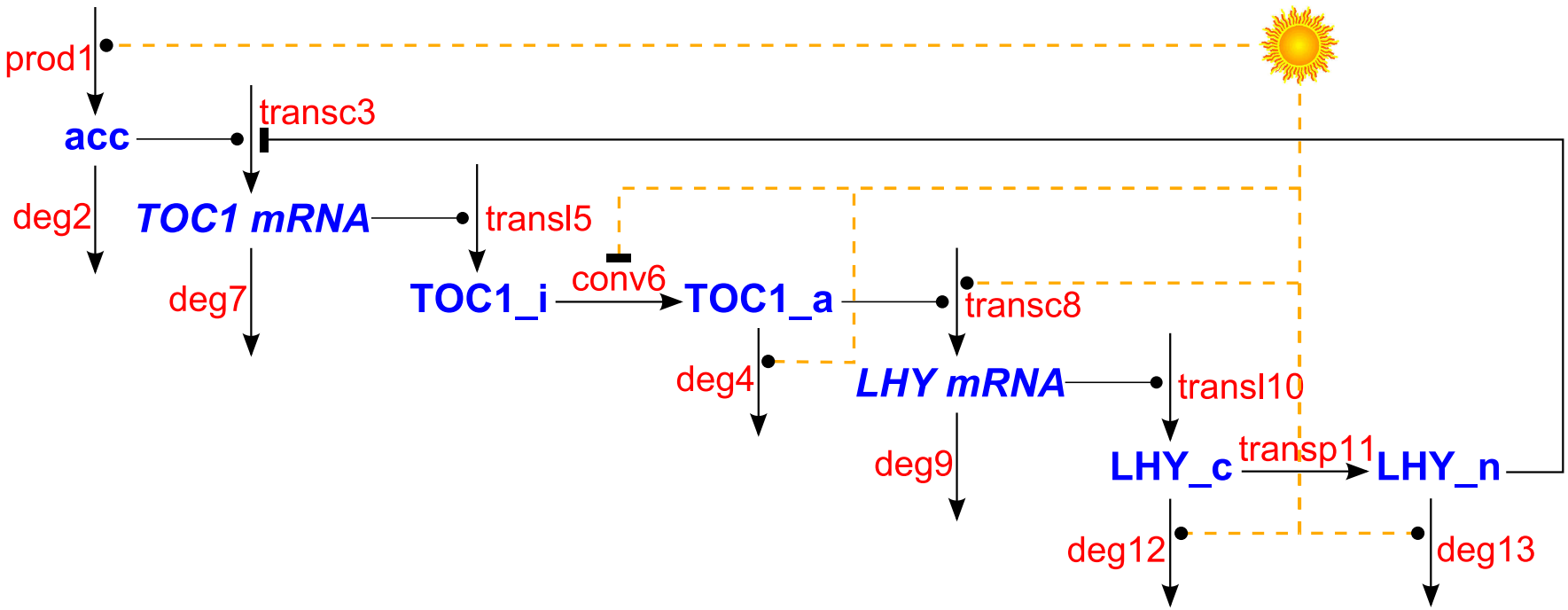
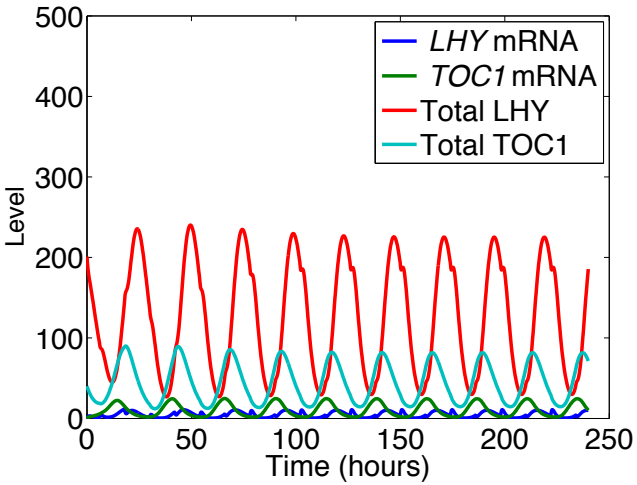
- two genes involved in circadian rhythm

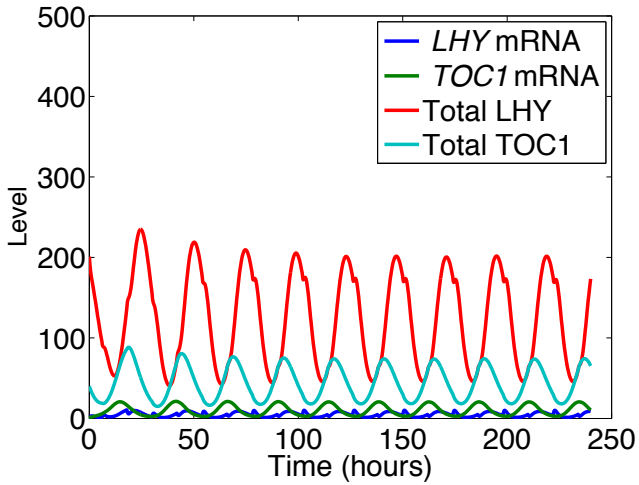


(Akman *et al*, FBTC 10, EPTCS 19, 2010)

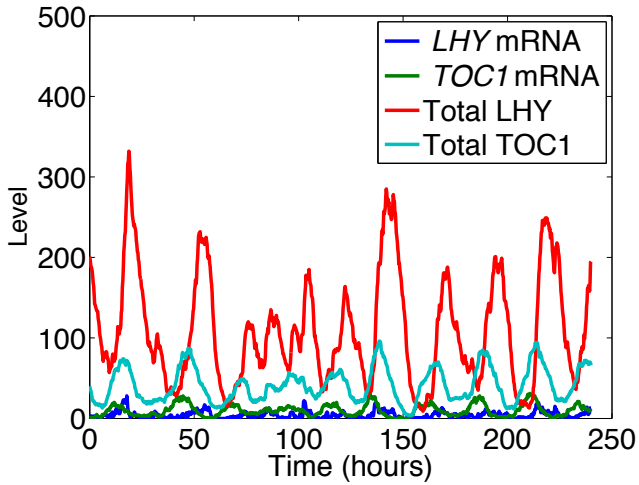
Circadian clock in Bio-PEPA: alternating light dark



(d) LD 12:12 – ODE



(e) LD 12:12 – average 10000 SSA runs



(f) LD 12:12 – single SSA run

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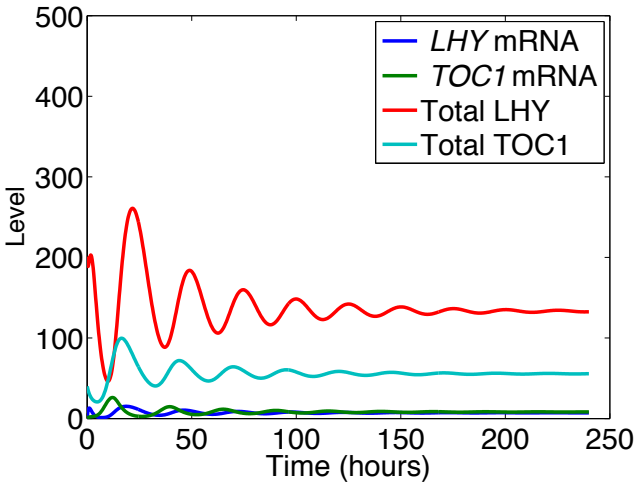
Circadian clock in Bio-PEPA: light only



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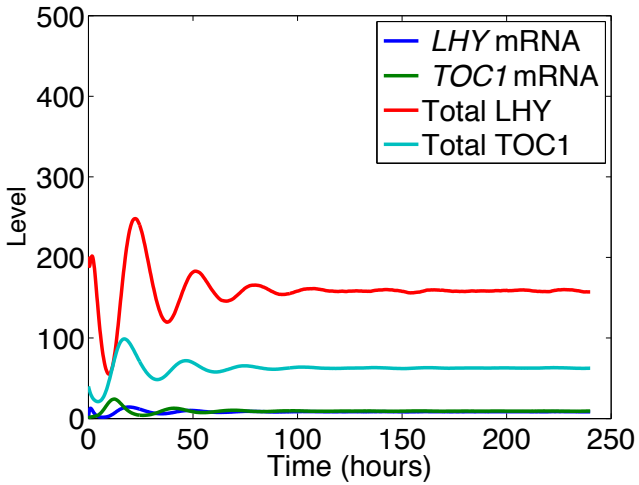

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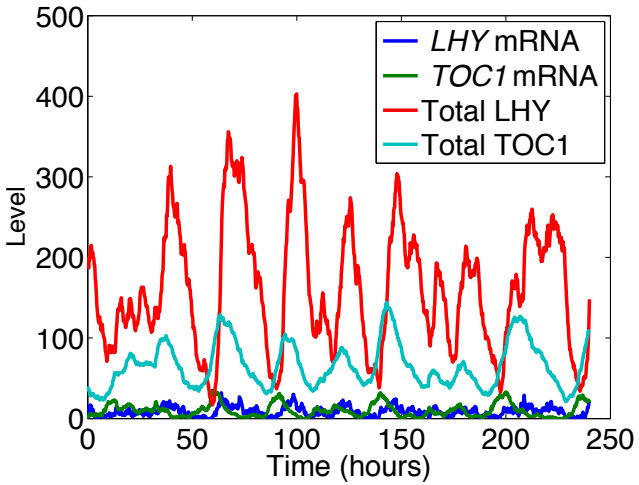

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Other Bio-PEPA case studies

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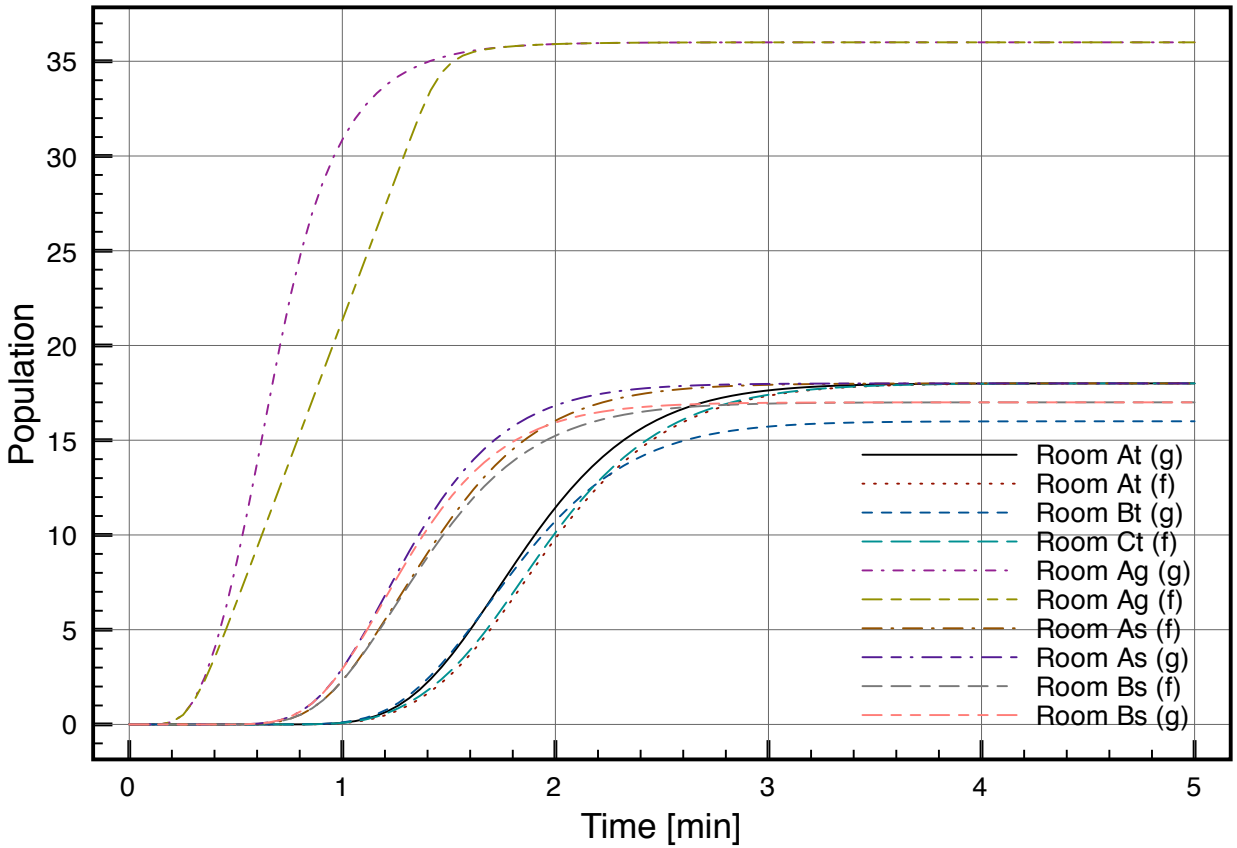
Emergency egress modelling in Bio-PEPA



(Massink *et al*, SEFM 2010)

Conclusion

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- how can Bio-PEPA contribute towards atlases?

Thank you

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- creation rate of active Src during basal behaviour
- binding rate for active Src and active FGFR
- time to pick up inactive Src in perinuclear region
- assume time taken in each loop fixed using calculations

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- enable the long recycling loop
- guess some parameters
- enable the doser and see what happens

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- need a more constrained form

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- well-defined Bio-PEPA species

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- well-defined Bio-PEPA model component with levels
  - minimum and maximum concentrations/number of molecules
  - fix step size, convert to minimum and maximum levels
  - species S: 0 to N_S levels

Example: reaction with enzyme

- $S + E \rightleftarrows SE \longrightarrow P + E$

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$$((\alpha,\kappa)\downarrow S)(\ell) \xrightarrow{(\alpha,[S:\downarrow(\ell,\kappa)])}_c S(\ell-\kappa) \quad \kappa \leq \ell \leq N_S$$

$$((\alpha,\kappa)\uparrow S)(\ell) \xrightarrow{(\alpha,[S:\uparrow(\ell,\kappa)])}_c S(\ell+\kappa) \quad 0 \leq \ell \leq N_S-\kappa$$

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Bio-PEPA semantics (continued)

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$$\frac{P \xrightarrow{(\alpha,v)}_c P' \quad Q \xrightarrow{(\alpha,u)}_c Q'}{P \underset{L}{\bowtie} Q \xrightarrow{(\alpha,v::u)}_c P' \underset{L}{\bowtie} Q'} \quad \alpha \in L$$

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- Bio-PEPA system: $\mathcal{P} = \langle \mathcal{T}, P \rangle$