Modelling protein trafficking: progress and challenges

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21 May 2012

Outline

Protein Trafficking

Modelling Biology

Process Algebras

Bio-PEPA

HYPE

Conclusions

Src protein

- non-receptor protein tyrosine kinase, member of Src family

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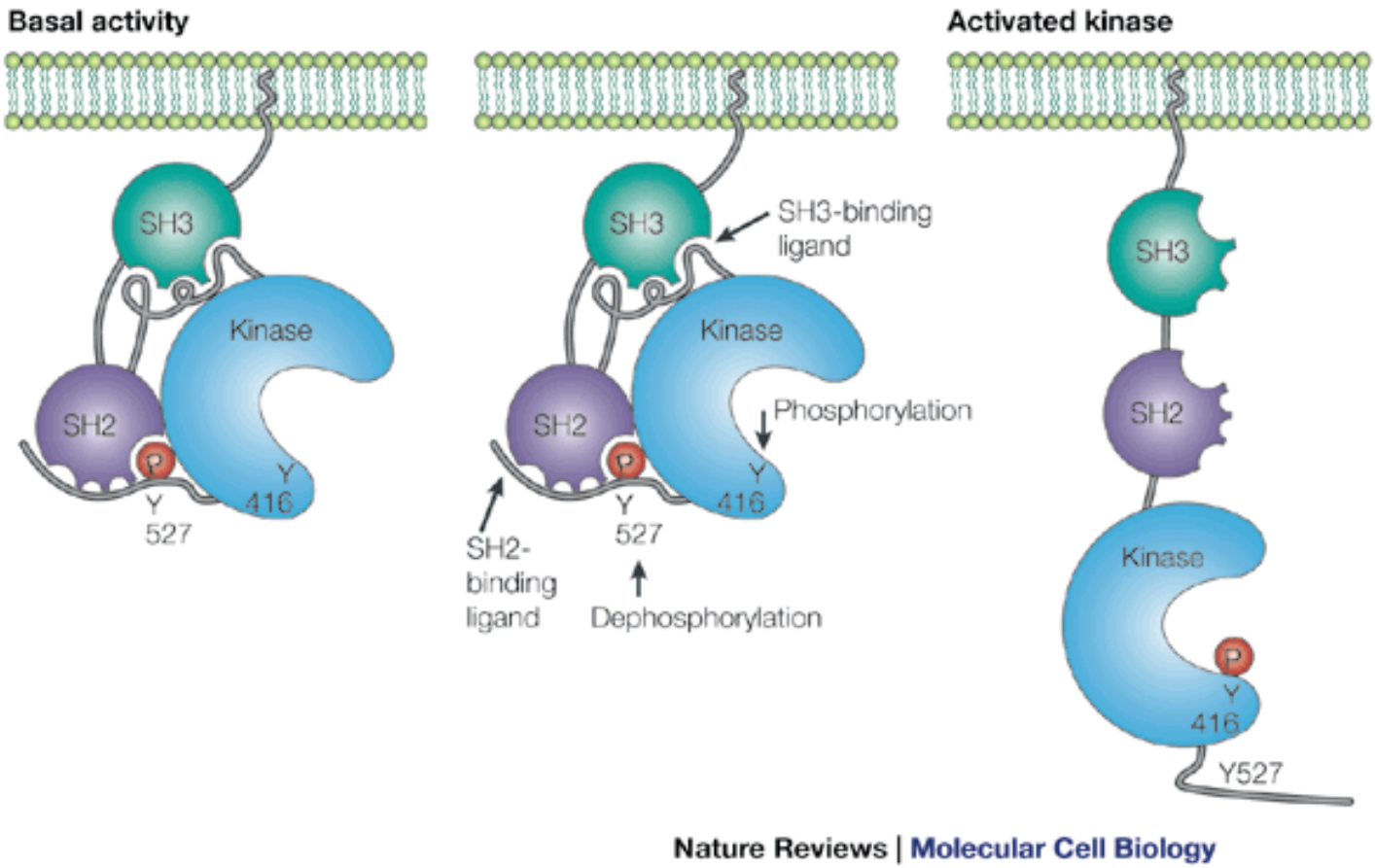
- in either inactive or active configuration

Src protein: inactive and active



(Martin, Nature Rev. Mol. Cell Biol. 2, 2001)

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- how does this happen?

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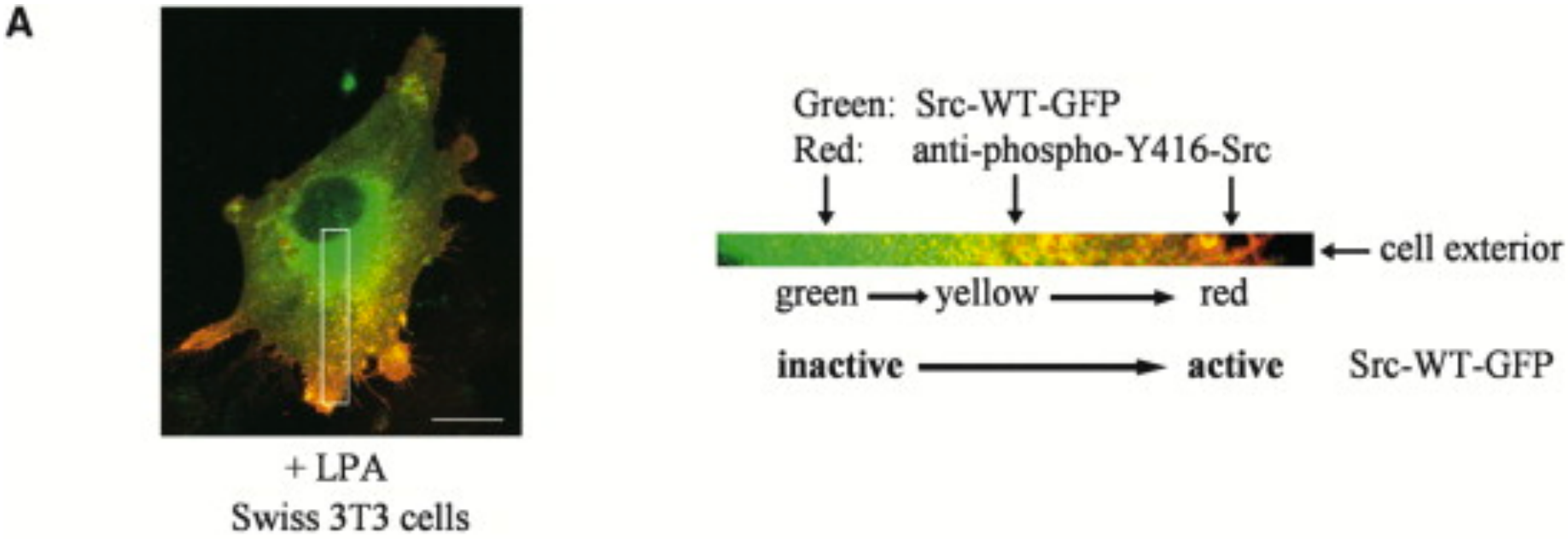
Mechanisms: gradient from inactive to active



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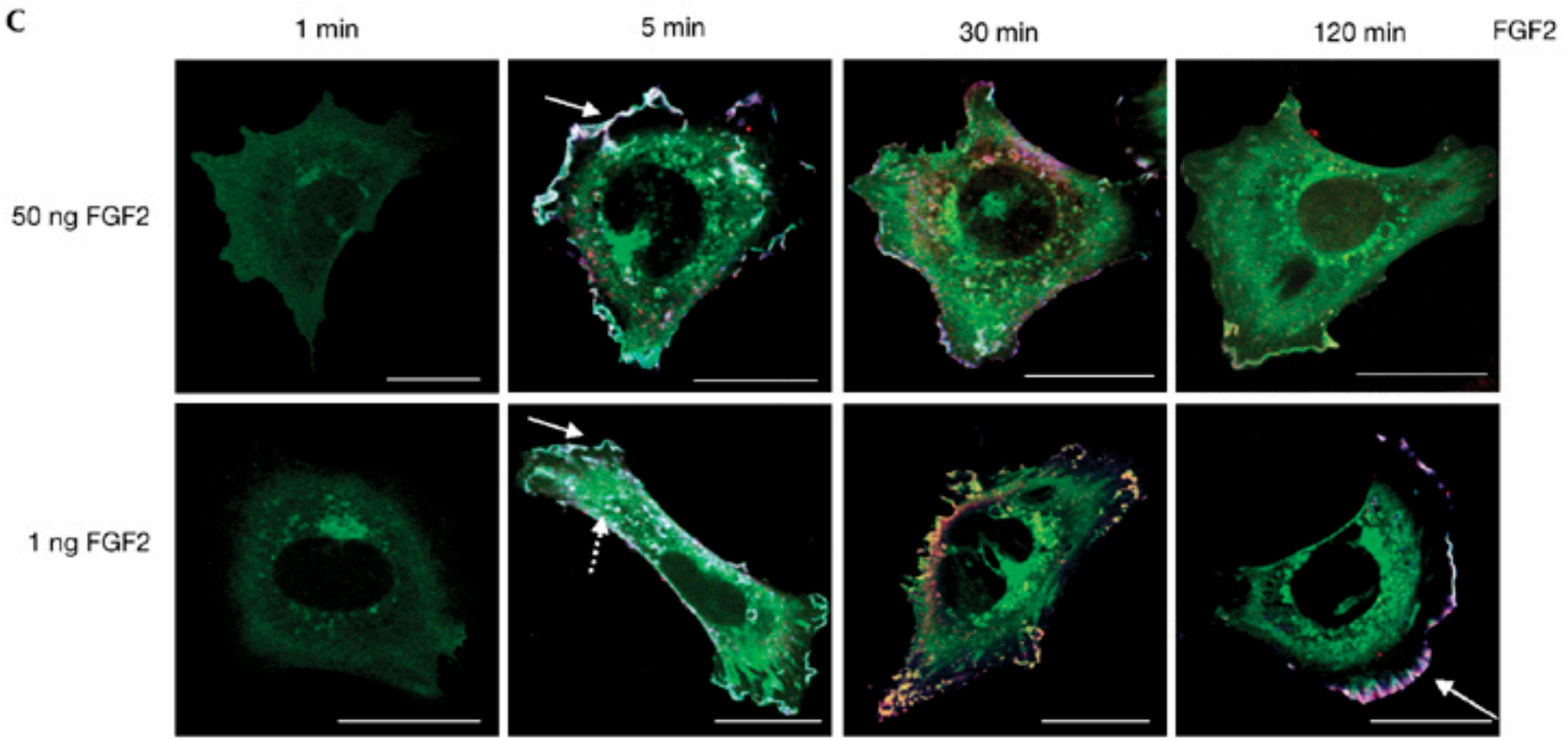
Mechanisms: persistence of response to FGF



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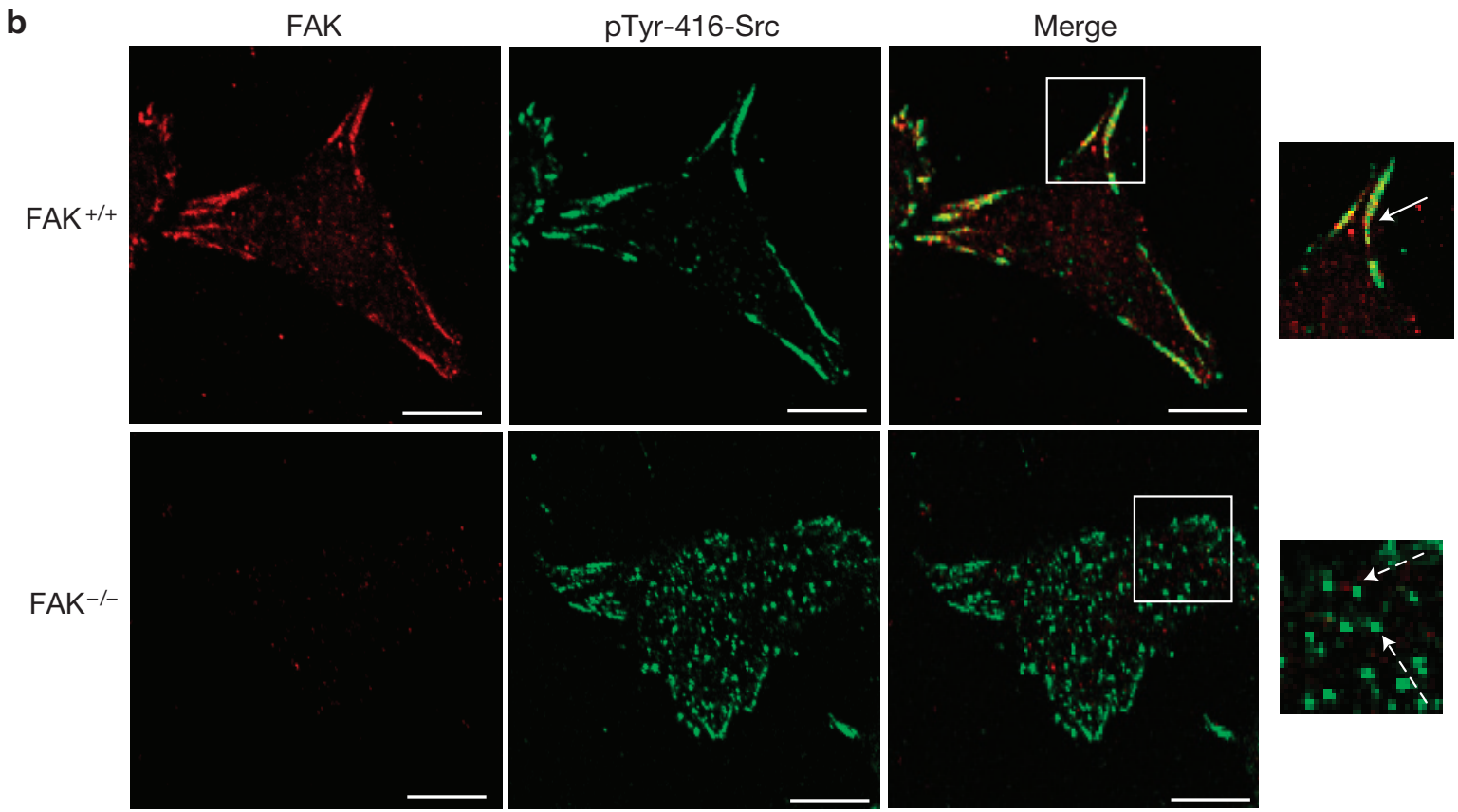
In cancerous cells, Src is sequestered in autophagosomes when FAK is absent, to avoid cell death as a result of excess Src not bound to FAK. (Sandilands *et al*, 2012)

Mechanisms: sequestration in autophagosomes



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Modelling protein trafficking

- modelling aspects

dynamic:	behaviour, change over time
	change on addition of FGF
spatial:	reactions happen in different parts of the cell
	molecules move within the cell
populations:	molecular species exist in reasonable numbers
	each species has a small number of possibilities

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- choice of formalism: process algebras
- modelling challenges

concrete:	generate hypotheses for further experiment
abstract:	modelling must be computationally feasible
data:	very limited

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  - cells have diameters of between $10\mu m$ and $100\mu m$
- both long and short recycling loops
  - time taken for half of short loop: assuming a distance of $10\mu m$ then 10 seconds
  - time take for half of long loop: assuming a distance of $20\mu m$ then 20 seconds

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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- Stochastic HYPE, a stochastic hybrid process algebra
  - developed by Bortolussi, Galpin and Hillston from HYPE
  - existing hybrid process algebras treated ODEs monolithically

Process algebras (continued)

- what is a process algebra?
  - compact and elegant formal language
  - behaviour given by semantics defined mathematically
  - classical process algebra: labelled transition systems
  - stochastic process algebra: continuous time Markov chains
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- why use a process algebra?
  - formalism to describe concurrent behaviour
  - provide an unambiguous and precise description
  - different analyses available from a single description
    simulation, model checking, CTMC analysis
  - they are mathematically beautiful

Bio-PEPA syntax

- species: reactions, stoichiometry, locations

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

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- process-as-species rather than process-as-molecules

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- rate function f_α uses information about the species and locations in the string v, together with the species and location information and rate parameters in calculating the actual rate of the reaction

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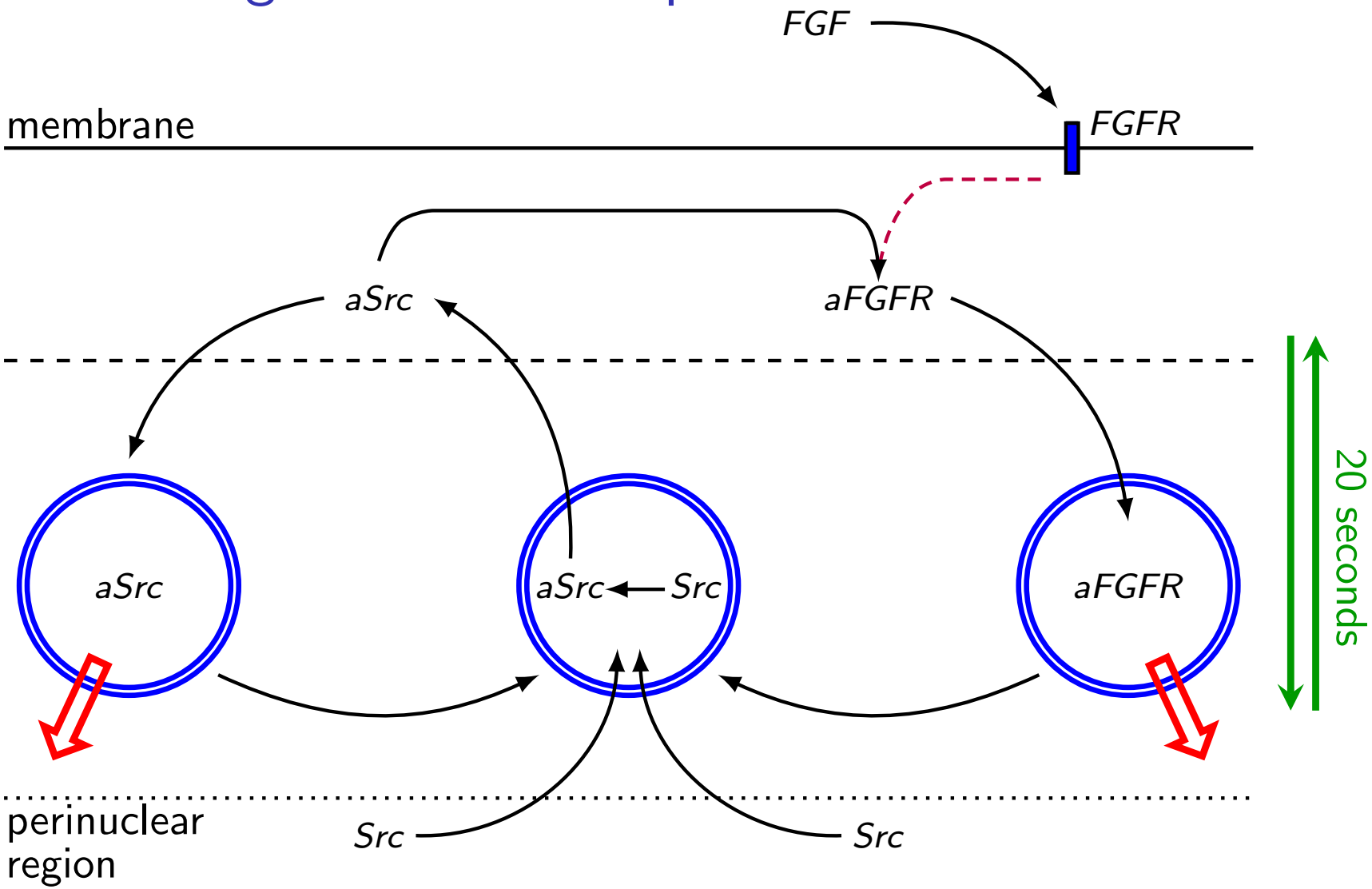
Src trafficking: combined loop model



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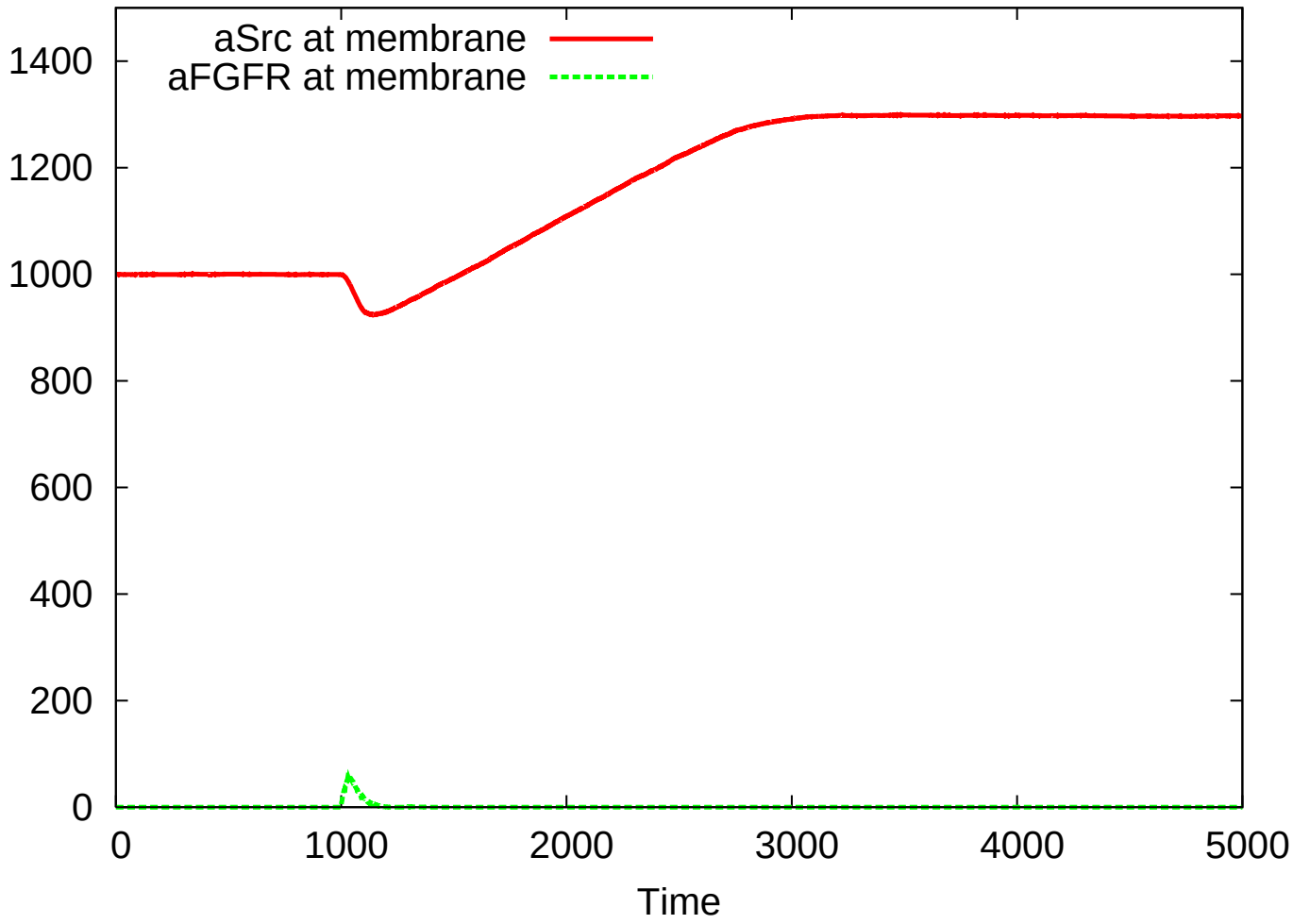
Combined loop trafficking model – results



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  - one short, one long

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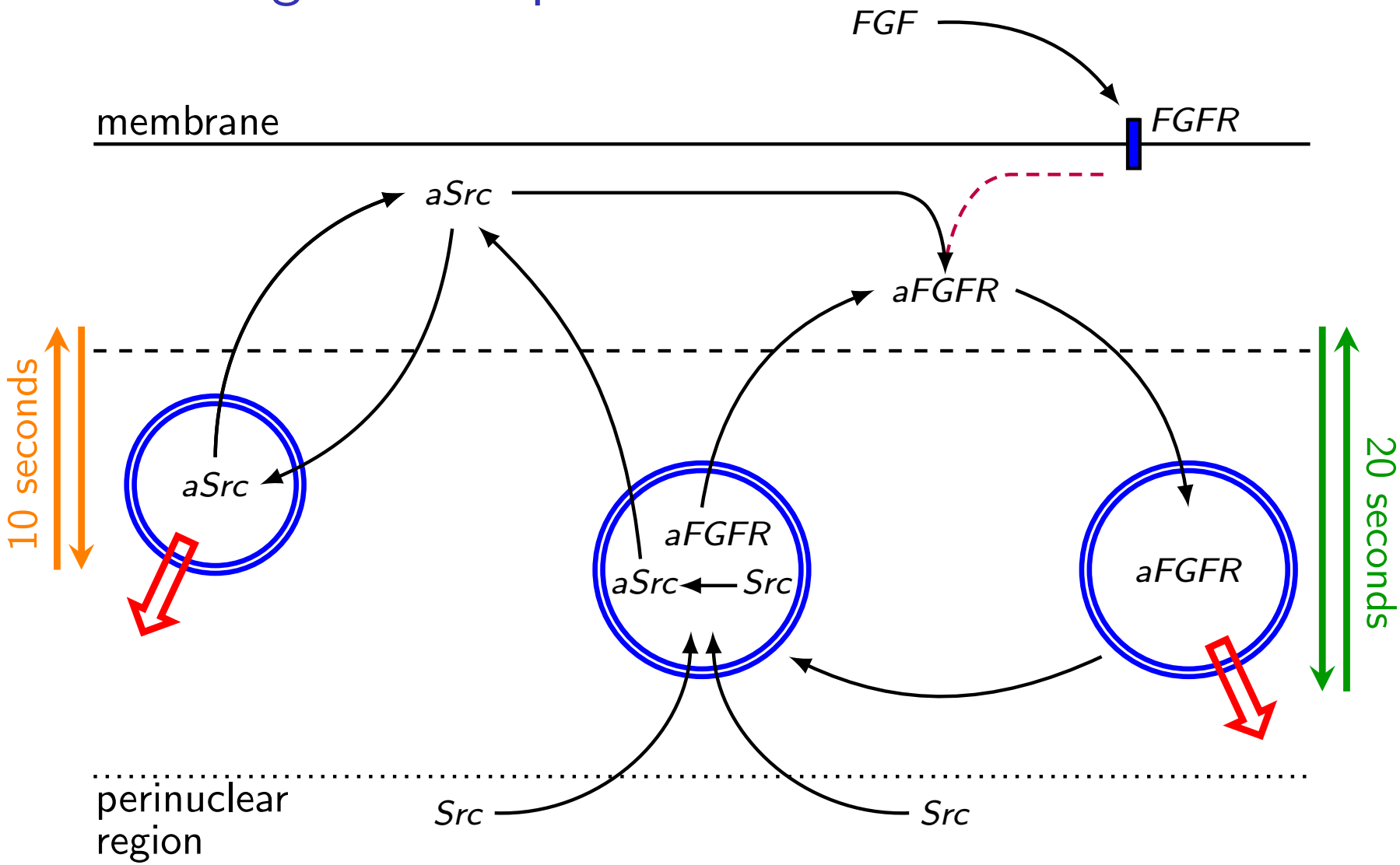

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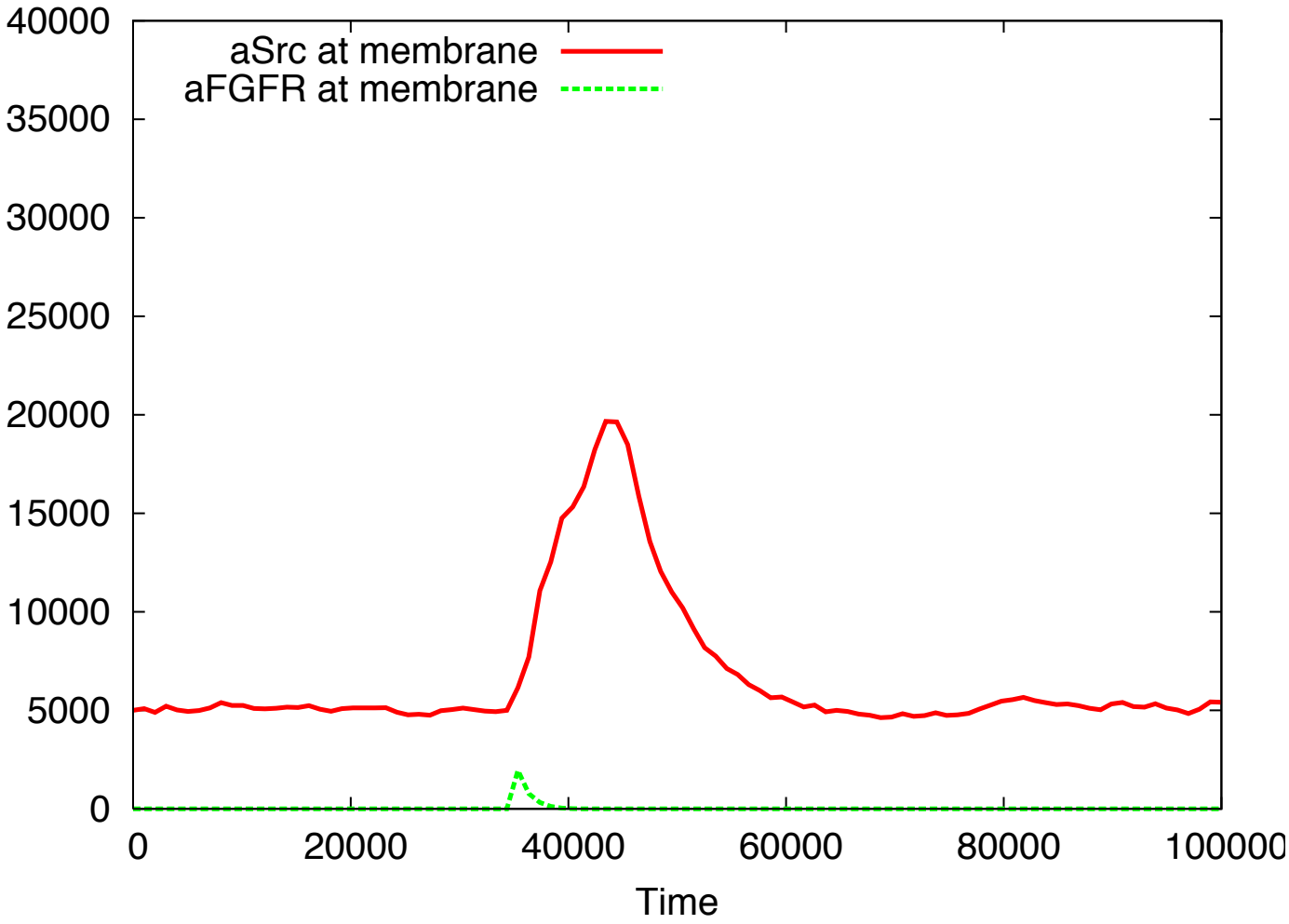

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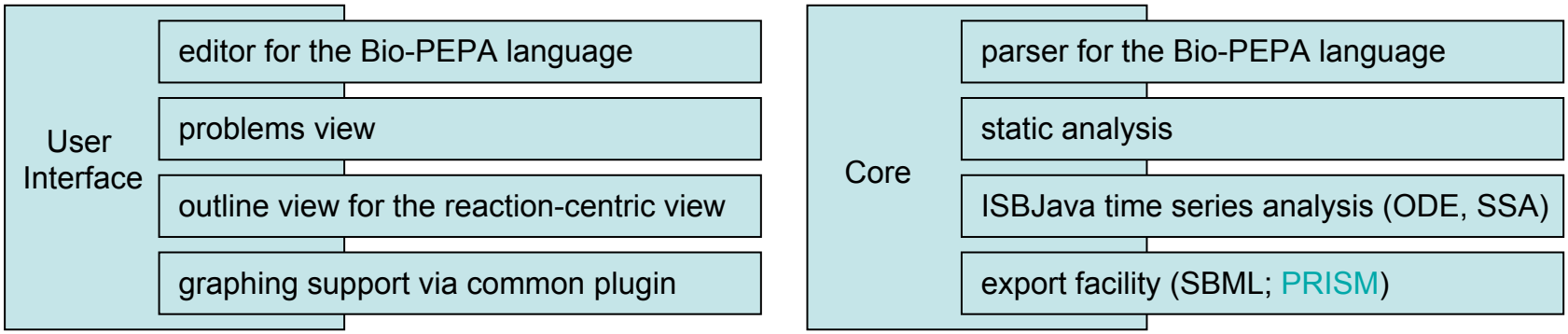

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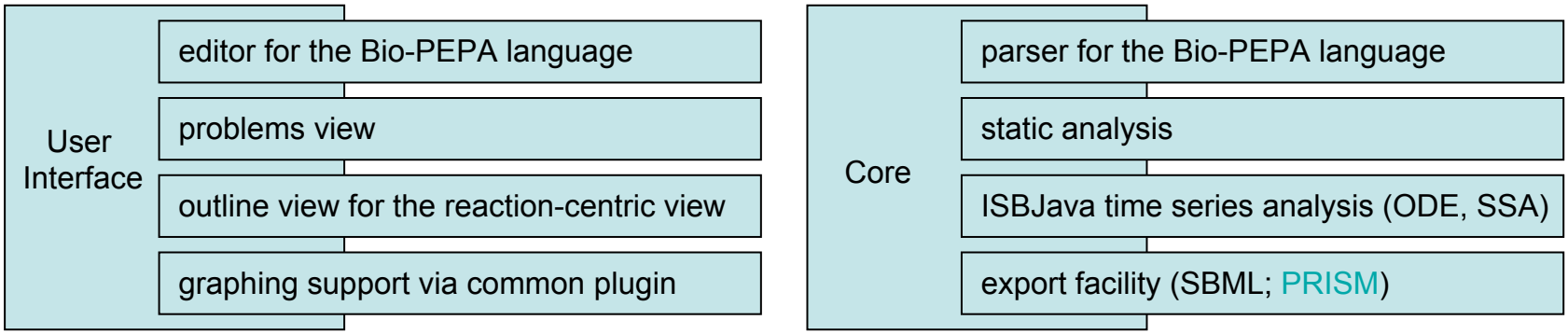
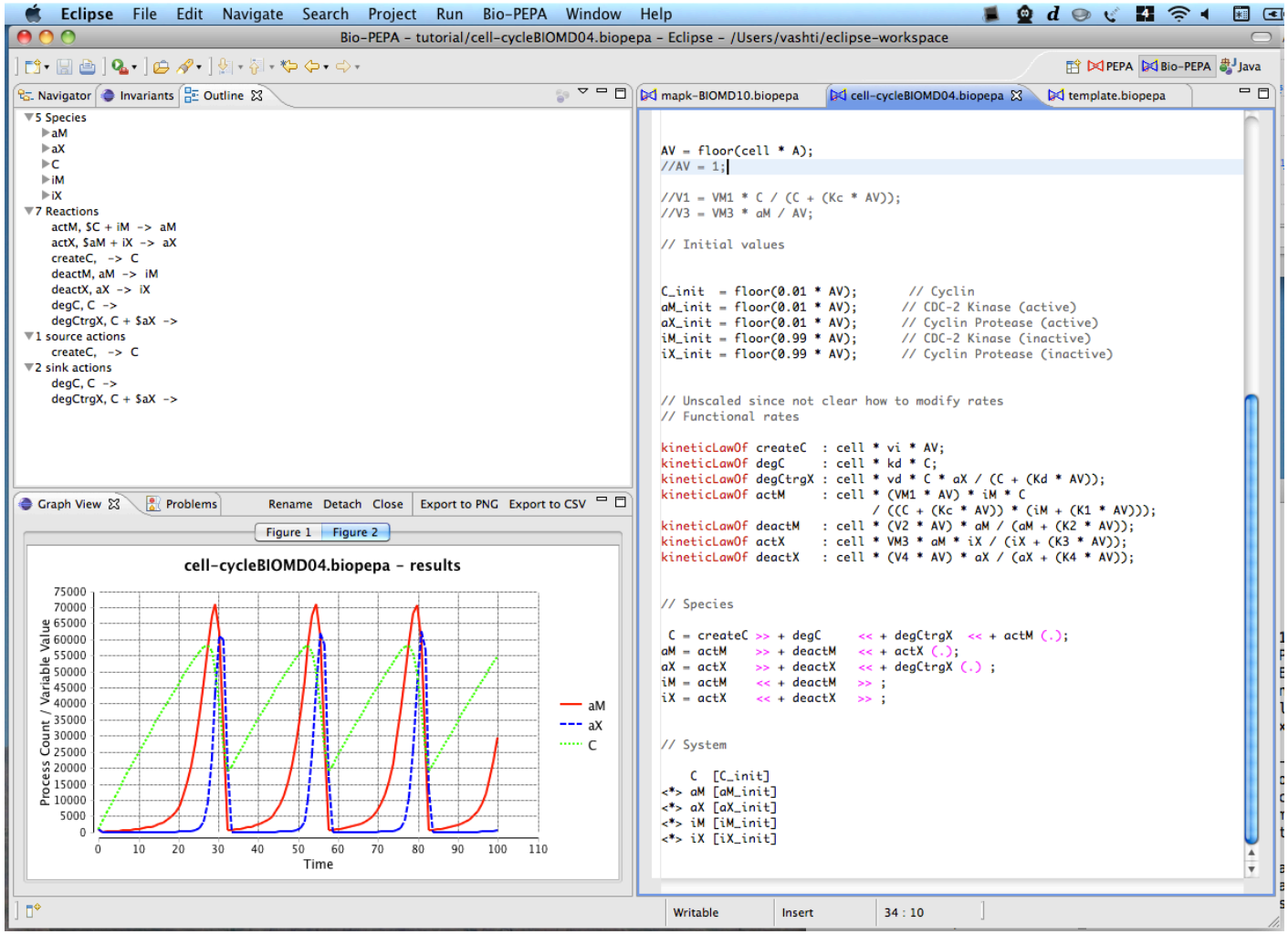


- available for download at `www.biopepa.org`
- case studies, publications, manuals

Bio-PEPA Eclipse Plug-in (continued)



Simplified Bio-PEPA model

- active Src at membrane

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- endsome in short recycling loop

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- model:

```
aSrc@mb[initial_aSrc_mb] <*> Endo_short@cyto[initial_Endo_short]
```

Simplified Bio-PEPA model

- active Src at membrane

```
aSrc@mb   =   (bind,1)   << aSrc@mb + (out_sh,150)   << aSrc@mb +
              (in_sh,75) >> aSrc@mb + (in_long,100) >> aSrc@mb;
```

- endsome in short recycling loop

```
Endo_short@cyto   =   (out_sh,1) >> Endo_short@cyto +
                      (in_sh,1)  << Endo_short@cyto + ... ;
```

- model:

```
aSrc@mb[initial_aSrc_mb] <*> Endo_short@cyto[initial_Endo_short]
```

- reactions

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

Stochastic HYPE

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subcomponents

$$(C_1(\mathcal{V}) \underset{*}{\bowtie} \cdots \underset{*}{\bowtie} C_n(\mathcal{V}))$$

Stochastic HYPE

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$$\left(C_1(\mathcal{V}) \underset{*}{\bowtie} \cdots \underset{*}{\bowtie} C_n(\mathcal{V})\right) \quad \underset{*}{\bowtie}$$

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$$\underbrace{\left(C_1(\mathcal{V}) \underset{*}{\bowtie} \cdots \underset{*}{\bowtie} C_n(\mathcal{V})\right)}_{\text{subcomponents}} \underset{*}{\bowtie} \underbrace{\left(Con_1 \underset{*}{\bowtie} \cdots \underset{*}{\bowtie} Con_m\right)}_{\text{controllers}}$$

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well-defined subcomponent

$$C(\mathcal{V}) \stackrel{def}{=} \sum_j \mathrm{a}_j : \alpha_j \,.\, C(\mathcal{V}) + \underline{\mathrm{init}} : \alpha \,.\, C(\mathcal{V})$$

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subcomponents are parameterised by variables

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events have event conditions: guards and resets

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influence names are mapped to variables

$$\mathrm{iv}(\iota_j) \in \mathcal{V}$$

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- each stochastic event represents something happening after time has passed, with a possible change of values: transport

Stochastic HYPE modelling

- output of model is a trajectory consisting of
  - continuous paths in $\mathbb{R}^n$
  - jumps/changes in values as events happen
  - piecewise deterministic Markov process
  - transition-driven stochastic hybrid automata

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- application to protein trafficking
  - work in progress
  - SimHyA simulator

The Repressilator

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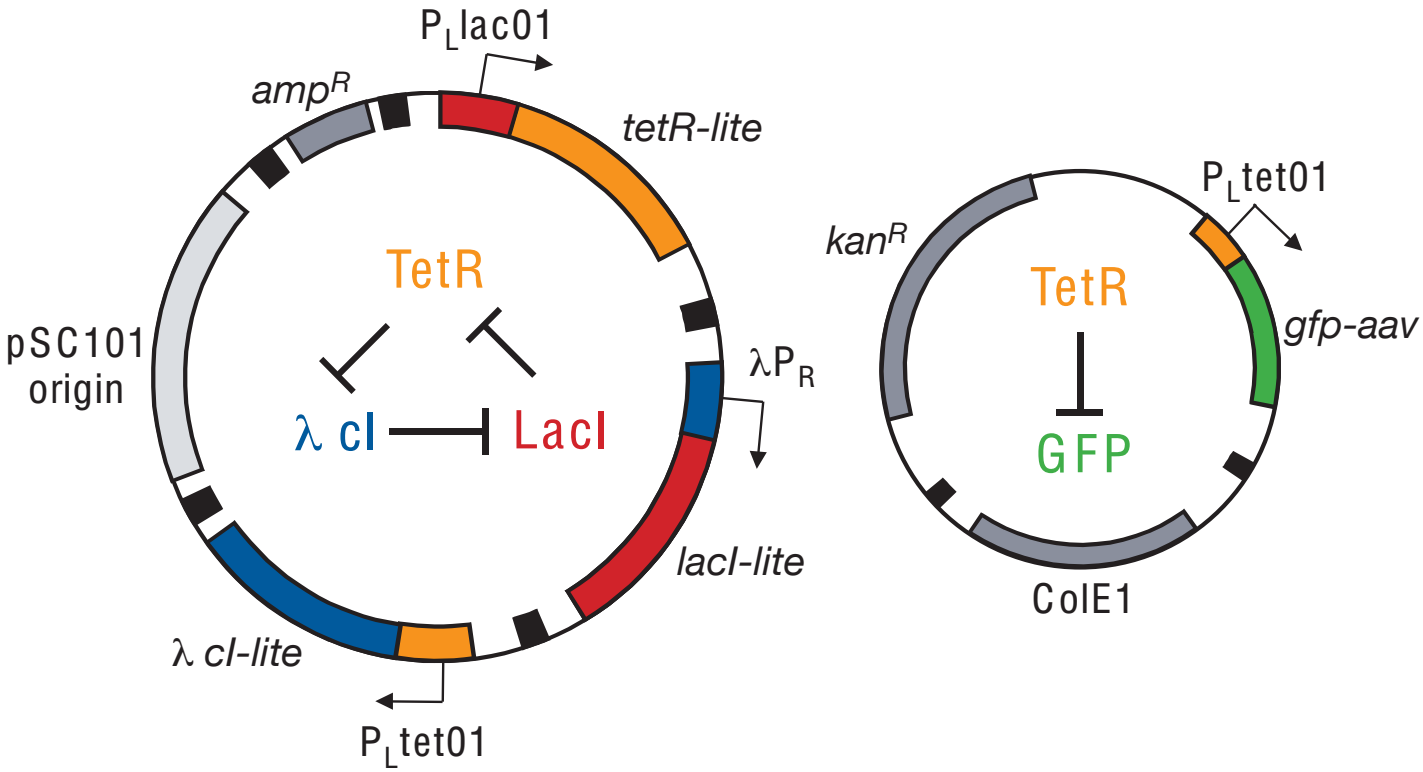
  - other gene cannot produce its protein
- quantities of proteins oscillate over time

The Repressilator



Elowitz and Leibler, Nature 403, 335-338.

The Repressilator

$Gene_A$

The Repressilator

$$Gene_A \xrightarrow[trs_A]{} mRNA_A$$

The Repressilator

$$Gene_A \xrightarrow[trs_A]{} mRNA_A \downarrow dm_A$$

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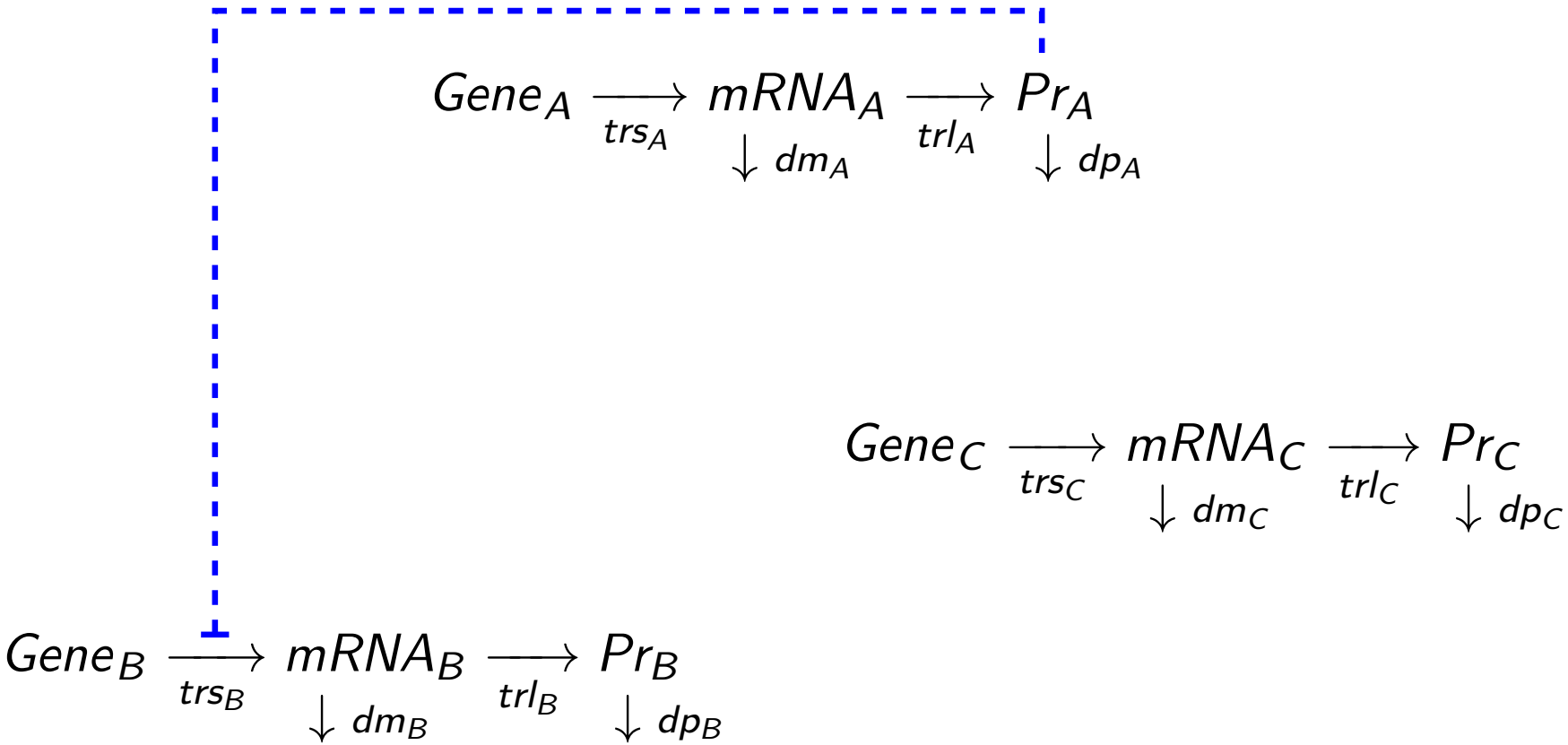
The Repressilator



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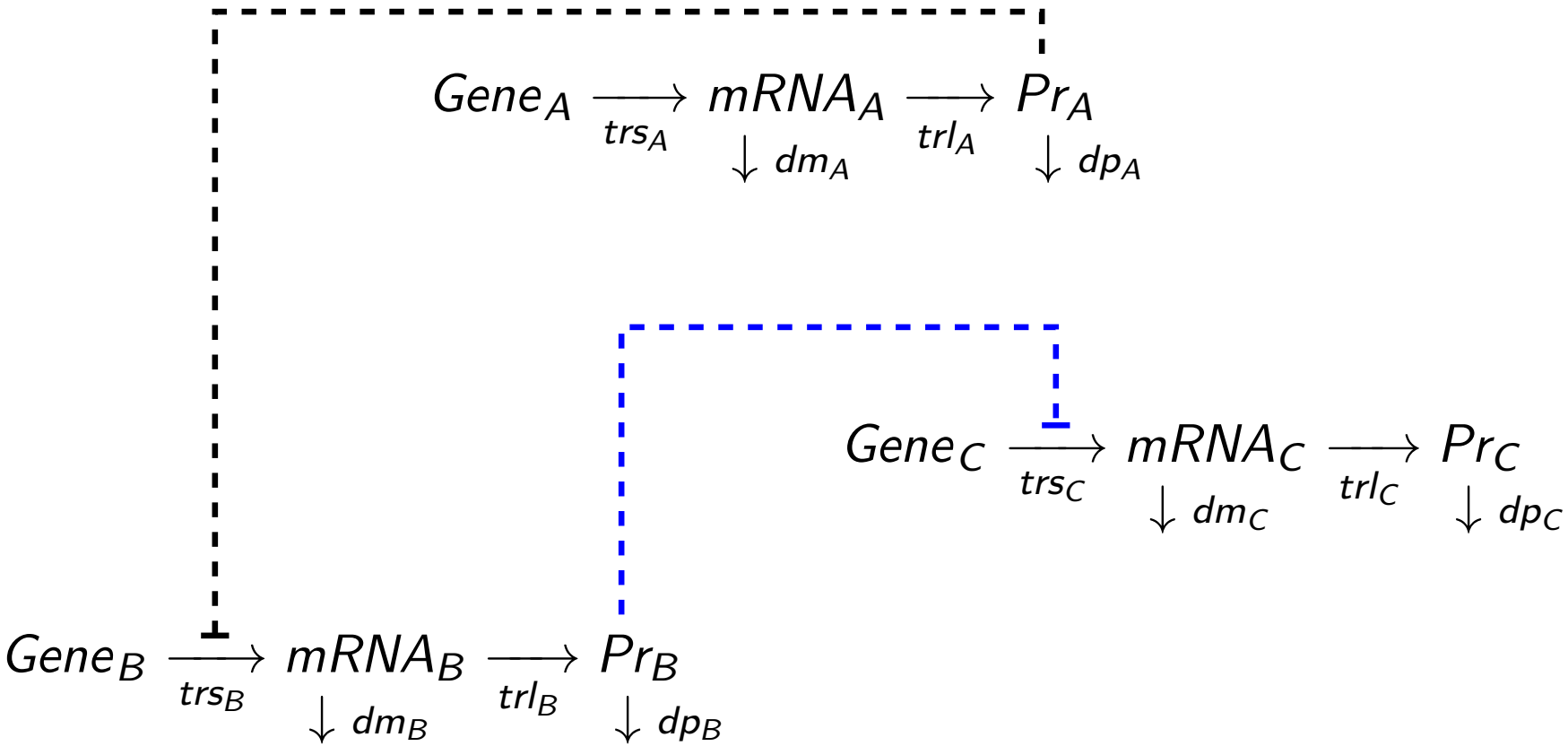

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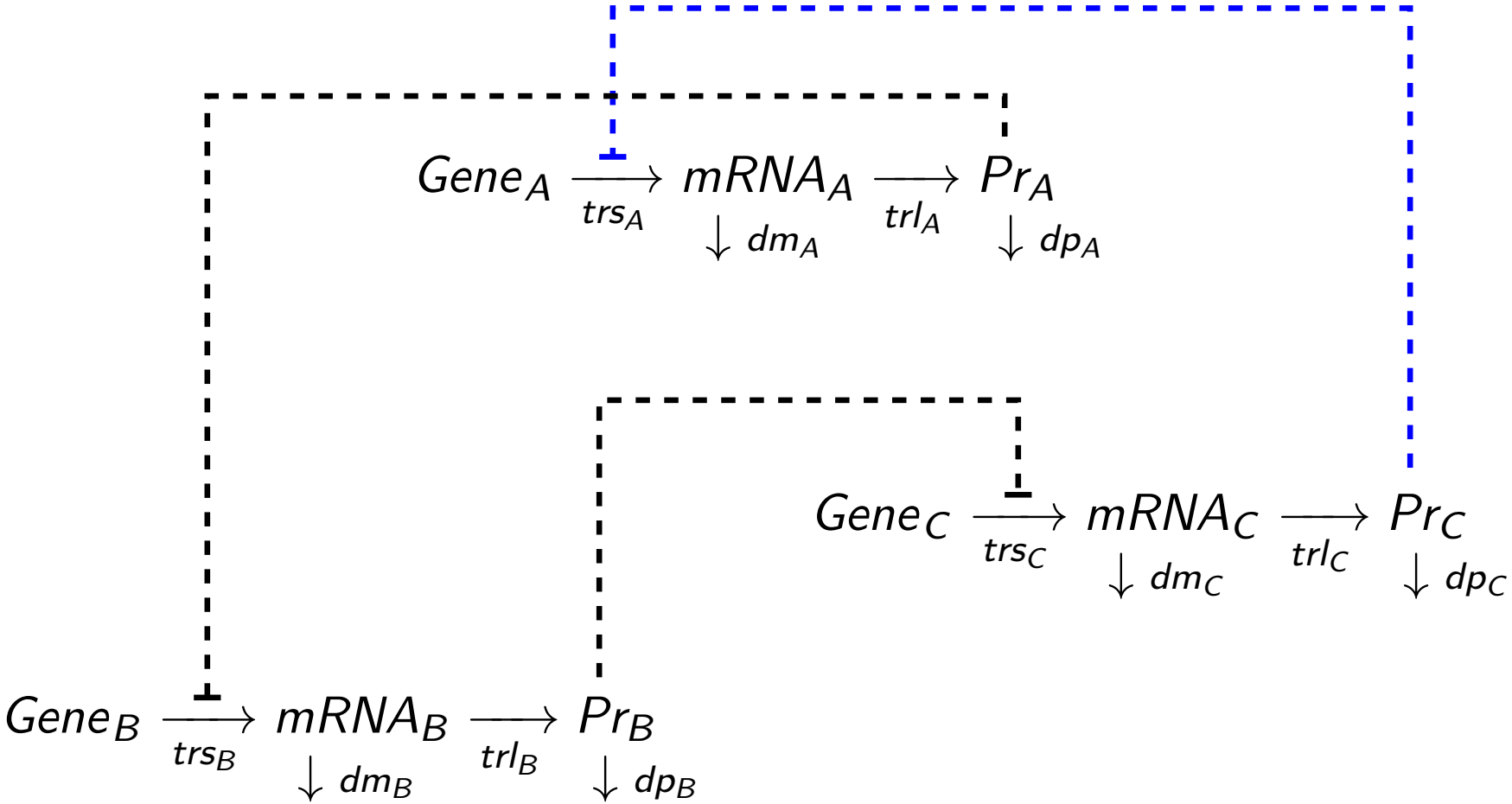

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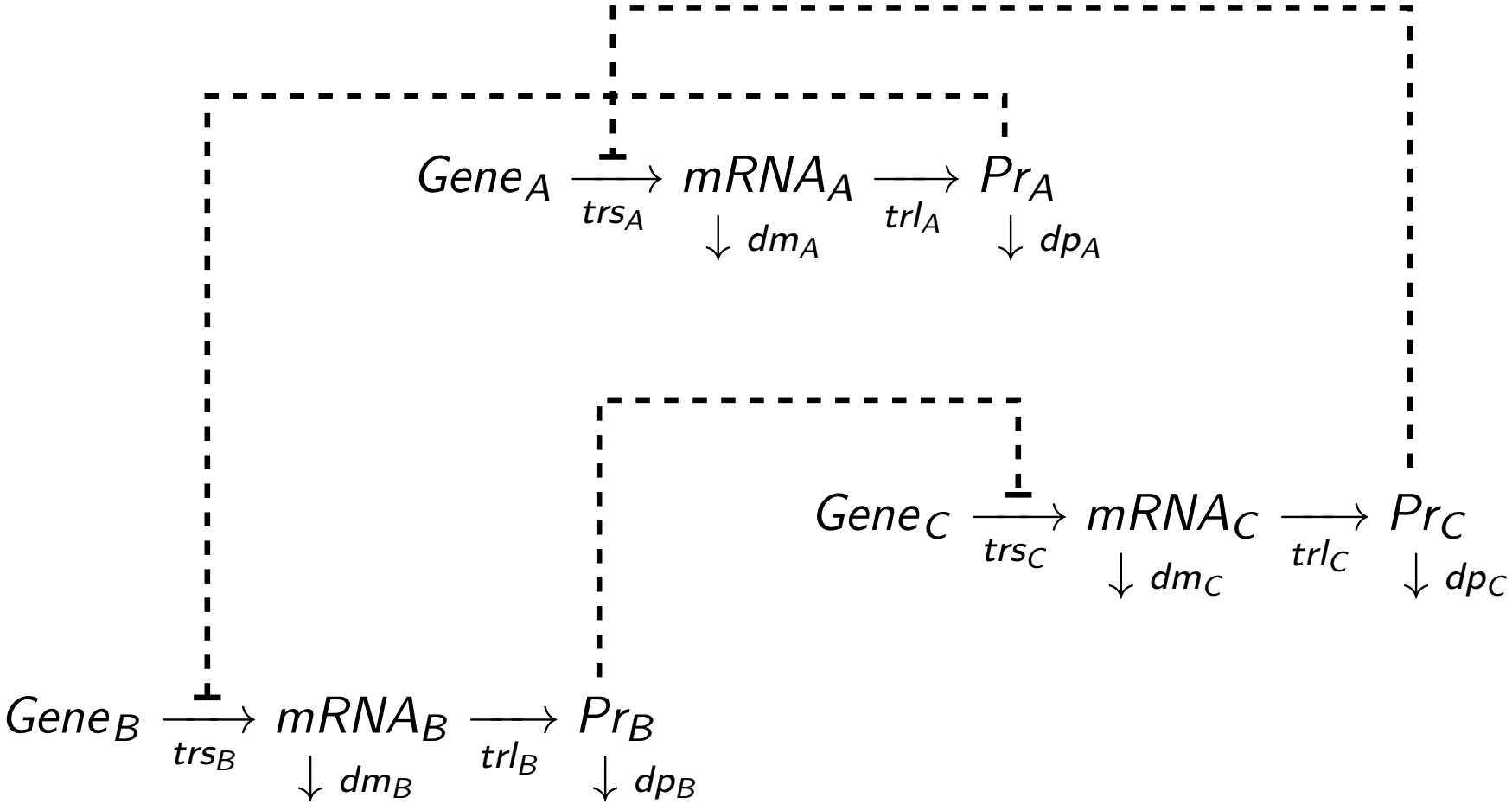

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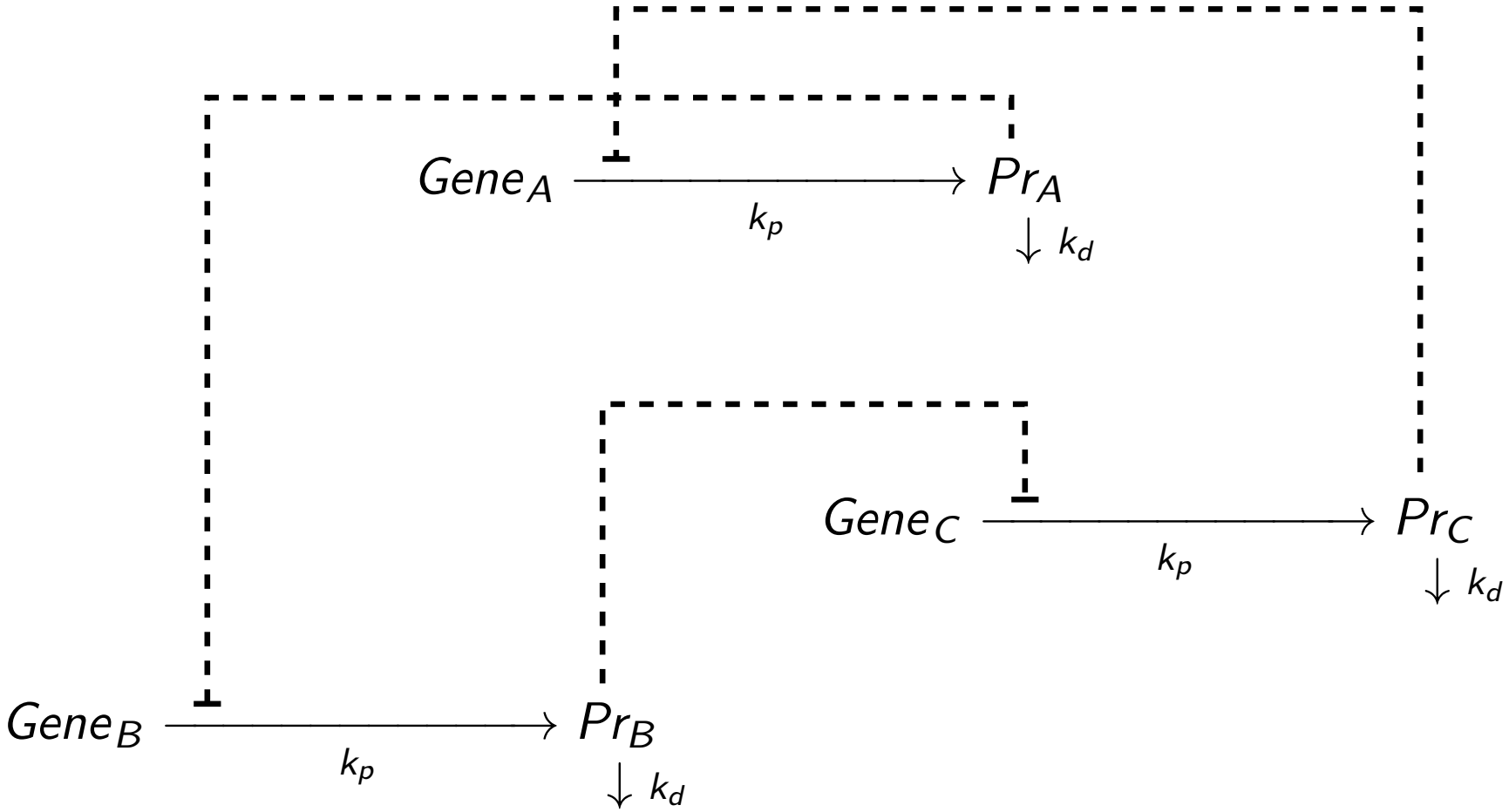

The Repressilator in HYPE

- degradation and production flows for Gene A:

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  $\text{ec}(\underline{\text{express}}_A) = (C \leq p, true)$

The Repressilator – protein levels over time

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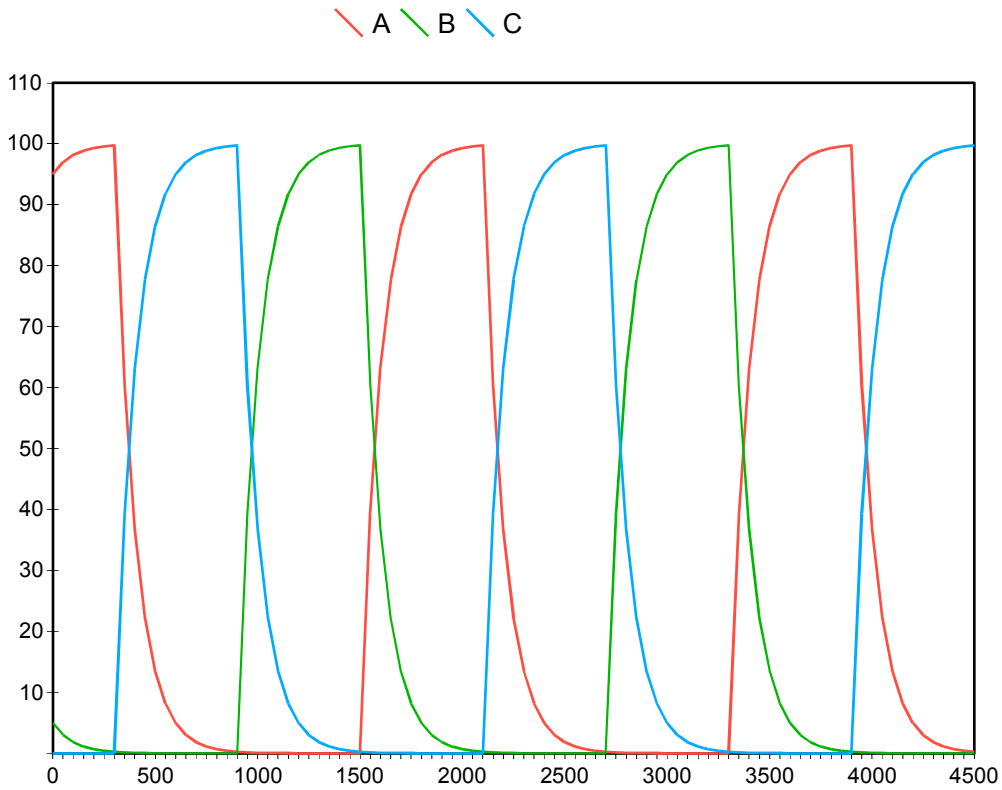

k_p=1.00 k_d=0.01

Conclusions

$$\text{Biology} + \text{Computing} = ??$$

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- using powerful mathematical models from computer science to model biology and in the longer term, to provide predictions
- major challenges
  - lack of data, models are often quasi-quantitative
  - getting right level of abstraction for useful models

Acknowledgements

PEPA Group
University of Edinburgh
Jane Hillston
Stephen Gilmore
Allan Clark
Maria Luisa Guerriero
Federica Ciocchetta
Adam Duguid

DMG
University of Trieste
Luca Bortolussi

Cancer Research UK
Edinburgh
Margaret Frame
Emma Sandilands

Thank you

Bio-PEPA syntax

- two-level syntax

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- sequential component, species

$$S ::= (\alpha, \kappa)\ \mathtt{op}\ S \mid S + S \qquad \mathtt{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\}$$

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- model component, system

$$P ::= S(\ell) \mid P \underset{L}{\bowtie} P$$

- need a more constrained form

Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

$$C \stackrel{def}{=} (\alpha_1, \kappa_1)\,\mathrm{op}_1\, C + \ldots + (\alpha_n, \kappa_n)\,\mathrm{op}_n\, C \text{ with all } \alpha_i\text{'s distinct}$$

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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

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- state vector (S, E, SE, P) and $N_S = N_E = N_{SE} = N_P = 3$

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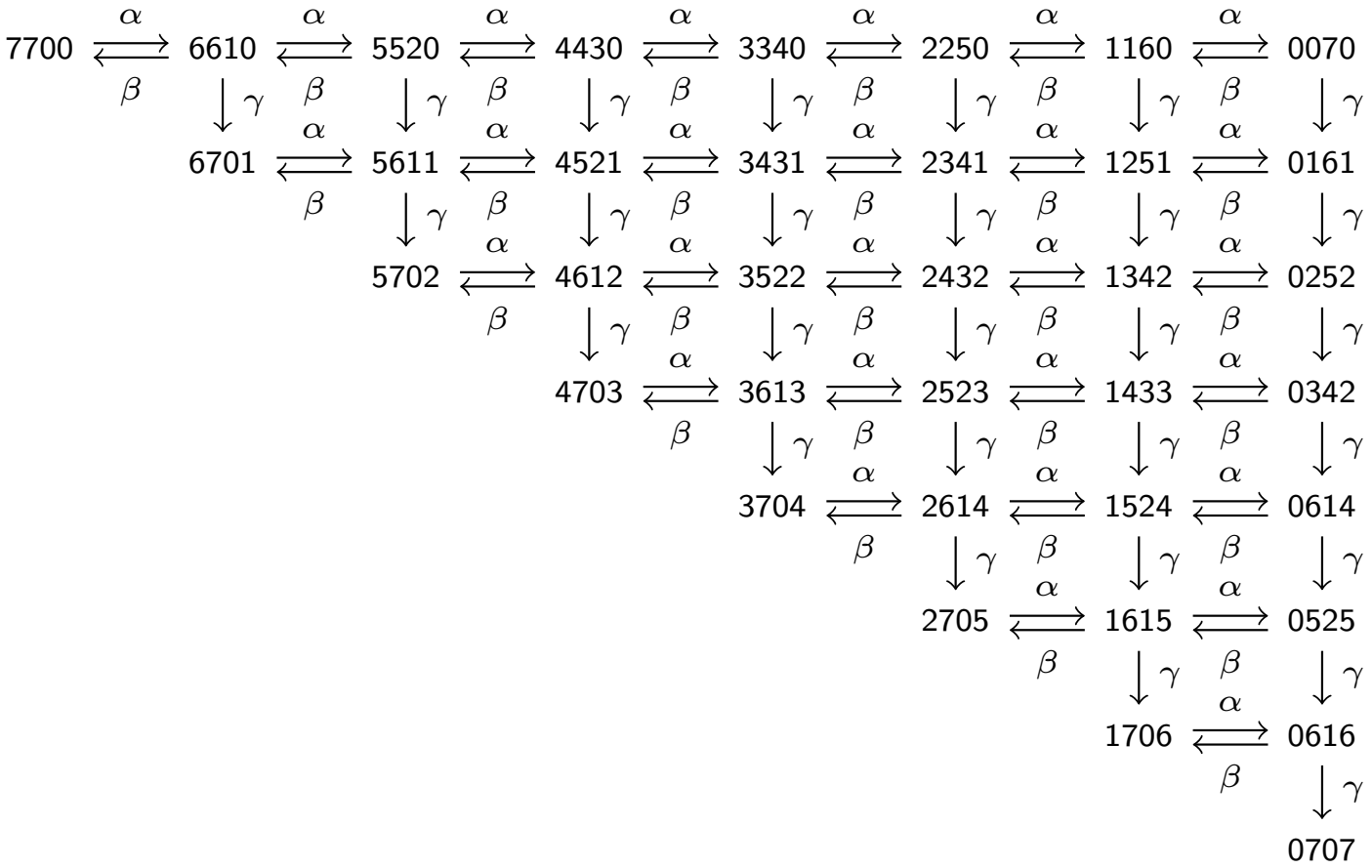
$$
\begin{array}{ccccccc}
(3,3,0,0) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (2,2,1,0) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (1,1,2,0) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (0,0,3,0) \\
 & & \downarrow \gamma & & \downarrow \gamma & & \downarrow \gamma \\
 & & (2,3,0,1) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (1,2,1,1) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (0,1,2,1) \\
 & & & & \downarrow \gamma & & \downarrow \gamma \\
 & & & & (1,3,0,2) & \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} & (0,2,1,2) \\
 & & & & & & \downarrow \gamma \\
 & & & & & & (0,3,0,3)
\end{array}
$$

Example: reaction with enzyme, max level 7

- state vector $S\ E\ SE\ P$ and $N_S = N_E = N_{SE} = N_P = 7$



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- initial parameters for species representing basal behaviour
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- input and output stoichiometry for each loop
  - short loop: input and output the same
  - long loop: output much larger than input
- 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

Parameters (continued)

- at least 13 unknown parameters – not so simple

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- enable short recycling loop only
- find parameters to balance short loop
  - 50% of active Src at membrane
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- 6 parameters not yet specified
- enable the long recycling loop
- guess some parameters
- enable the doser and see what happens