Formal modelling of biological systems

Vashti Galpin

Laboratory for Foundations of Computer Science
School of Informatics
University of Edinburgh

(Joint work with Jane Hillston)

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Outline

Process algebras

Bio-PEPA

Semantics

Enzyme example

Hybrid approach

Src trafficking

Conclusions

Process algebras – history

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    - Robin Milner: CCS, operational
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- similar ideas, all compositional
- compact, elegant formal language

Prefix $a.P$ Choice $P_1 + P_2$ Parallel $P_1 \parallel P_2$ $\ldots$

Process algebras – history (continued)

- operational semantics gives labelled transition system

$$a.P \xrightarrow{a} P$$

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P_1 \parallel P_2 \xrightarrow{f(a_1,a_2)} Q_1 \parallel Q_2 & \text{whenever} & P_1 \xrightarrow{a_1} Q_1,\, P_2 \xrightarrow{a_2} Q_2
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- no notion of time, only ordering, so various extensions

Process algebras – stochastic

- addition of random time
  - interleaved with actions
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- semantics given as continuous-time Markov chain
- fluid dynamics: semantics as ordinary differential equations
- applied to biological modelling
  - reagent-centric and reaction-centric styles
  - limitations: stoichiometry, functional rates
- Bio-PEPA: developed by Ciocchetta and Hillston (2009)

Systems biology modelling

- general approach (Regev, Silverman, Shapiro)

Concurrency	**Molecular biology**	**Metabolism**	**Signal transduction**
Concurrent computational processes	molecules	enzymes and metabolites	interacting proteins
Synchronous communication	molecular interaction	binding and catalysis	binding and catalysis

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- stochastic model or deterministic model?
- aims of modelling: good enough and practical enough

Bio-PEPA syntax

- species: reactions, stoichiometry, locations

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

where $\mathtt{op}_i \in \{\downarrow, \uparrow, \oplus, \ominus, \odot\}$

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$\mathcal{L}$ compartments and locations, dimensionality, sizes

$\mathcal{N}$ species quantities, minimums, maximums, step size

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

Example: reaction with enzyme

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- operational semantics for capability relation $\rightarrow_c$

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

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Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in M$

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

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- operational semantics for stochastic relation $\rightarrow_s$

$$\frac{P \xrightarrow{(\alpha,v)}_c P'}{\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, Comp, P\rangle \xrightarrow{(\alpha, f_\alpha(v,\mathcal{V},\mathcal{N},\mathcal{K})/h)}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, Comp, P'\rangle}$$

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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

Example: reaction with enzyme, max level 3

- state vector (S, E, C, P) and $N_S = N_E = N_C = N_P = 3$

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$$\begin{tikzcd}
(3,3,0,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (2,2,1,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & (1,1,2,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & (0,0,3,0) \arrow[d, "\gamma"'] \\
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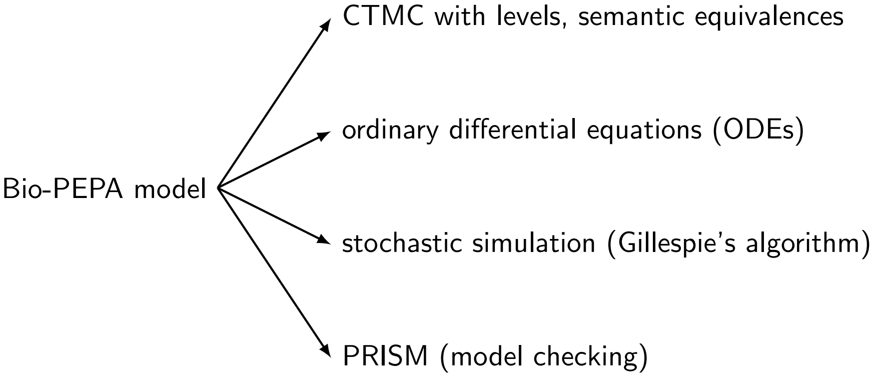
 & & (1,3,0,2) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (0,2,1,2) \arrow[d, "\gamma"'] \\
 & & & (0,3,0,3)
\end{tikzcd}$$

Example: reaction with enzyme, max level 7

- state vector $S\ E\ C\ P$ and $N_S = N_E = N_C = N_P = 7$

$$\begin{tikzcd}
7700 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 6610 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 5520 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 4430 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 3340 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 2250 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 1160 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0070 \arrow[d, "\gamma"'] \\
 & 6701 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 5611 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 4521 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 3431 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 2341 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 1251 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0161 \arrow[d, "\gamma"'] \\
 & & 5702 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 4612 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 3522 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 2432 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 1342 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0252 \arrow[d, "\gamma"'] \\
 & & & 4703 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 3613 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 2523 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 1433 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0342 \arrow[d, "\gamma"'] \\
 & & & & 3704 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 2614 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 1524 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0614 \arrow[d, "\gamma"'] \\
 & & & & & 2705 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 1615 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"'] & 0525 \arrow[d, "\gamma"'] \\
 & & & & & & 1706 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 0616 \arrow[d, "\gamma"'] \\
 & & & & & & & 0707
\end{tikzcd}$$

Different types of analysis



Bio-PEPA model

CTMC with levels, semantic equivalences

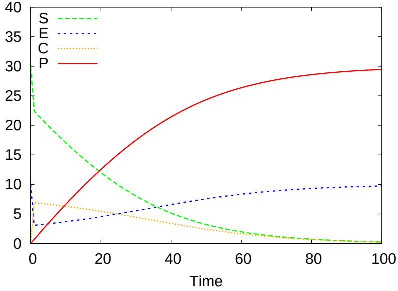
ordinary differential equations (ODEs)

stochastic simulation (Gillespie's algorithm)

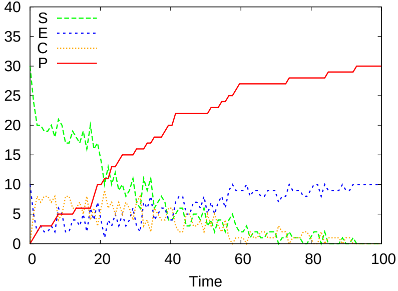
PRISM (model checking)

Deterministic versus stochastic simulation

deterministic trace



single stochastic trace



$$S(30) \underset{*}{\bowtie} E(10) \underset{*}{\bowtie} C(0) \underset{*}{\bowtie} P(0)$$
$$k_{\alpha} = 10 \quad k_{\beta} = 100 \quad k_{\gamma} = 0.1$$

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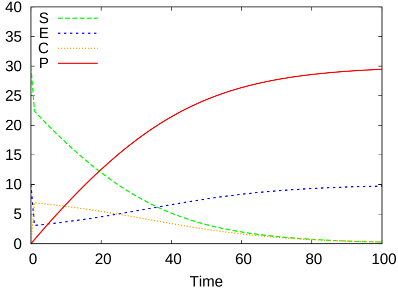
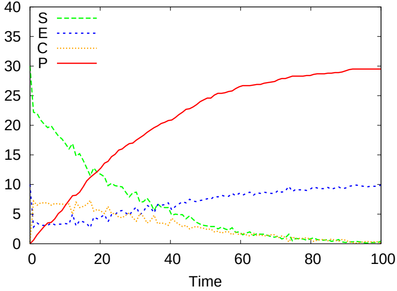


average of 10 stochastic traces



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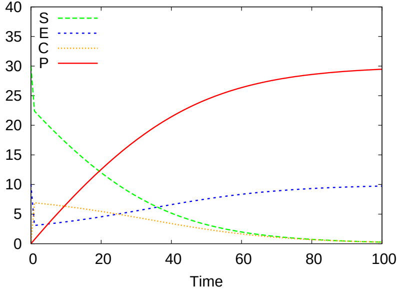
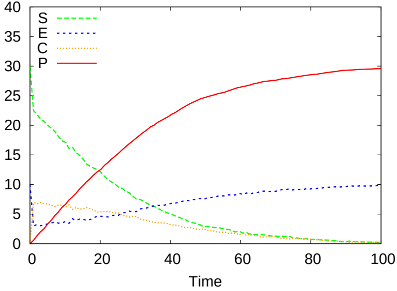


average of 100 stochastic traces



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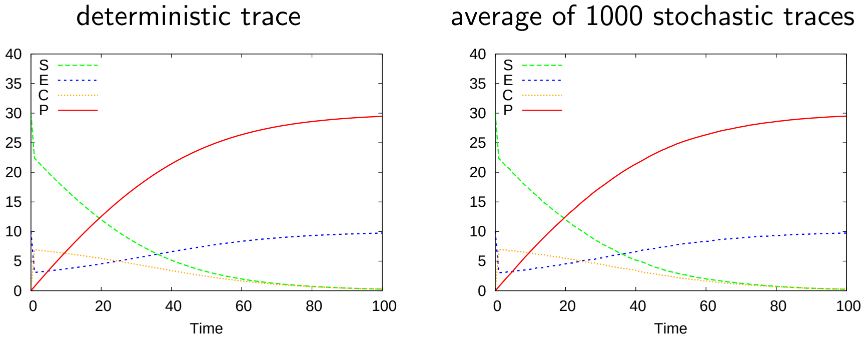

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Bio-PEPA Eclipse Plug-in

- software tool for Bio-PEPA modelling

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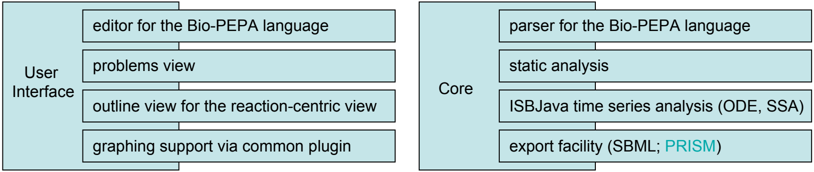
- Eclipse front-end and separate back-end library



User Interface

- editor for the Bio-PEPA language
- problems view
- outline view for the reaction-centric view
- graphing support via common plugin

Core

- parser for the Bio-PEPA language
- static analysis
- ISBJava time series analysis (ODE, SSA)
- export facility (SBML; PRISM)

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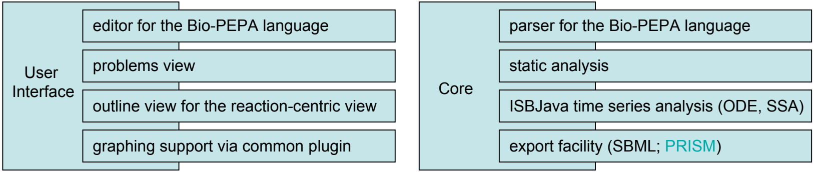

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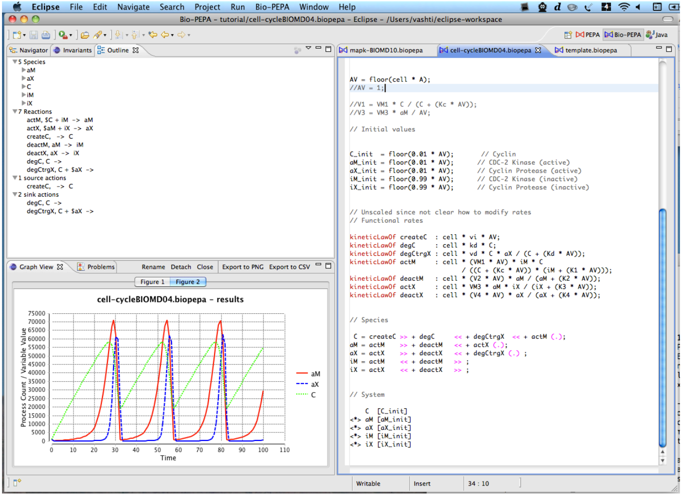
- available for download at `www.biopepa.org`
- case studies, publications, manuals

Bio-PEPA Eclipse Plug-in (continued)


Eclipse File Edit Navigate Search Project Run Bio-PEPA Window Help
Bio-PEPA - tutorial/cell-cycleBIOMD04.biopepa - Eclipse - /Users/vashti/eclipse-workspace
PEPA Bio-PEPA Java
Navigator Invariants Outline
mapk-BIOMD10.biopepa cell-cycleBIOMD04.biopepa template.biopepa
Graph View Problems Rename Detach Close Export to PNG Export to CSV
Figure 1 Figure 2
cell-cycleBIOMD04.biopepa - results
Process Count / Variable Value
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0 10 20 30 40 50 60 70 80 90 100 110
Time
aM
aX
C
Writable Insert 34 : 10

```
▼5 Species
   ▶aM
   ▶aX
   ▶C
   ▶iM
   ▶iX
▼7 Reactions
   actM, $C + iM  ->  aM
   actX, $aM + iX  ->  aX
   createC,   ->  C
   deactM, aM  ->  iM
   deactX, aX  ->  iX
   degC, C  ->
   degCtrgX, C + $aX  ->
▼1 source actions
   createC,   ->  C
▼2 sink actions
   degC, C  ->
   degCtrgX, C + $aX  ->
```

```
AV = floor(cell * A);
//AV = 1;

//V1 = VM1 * C / (C + (Kc * AV));
//V3 = VM3 * aM / AV;

// Initial values


C_init  = floor(0.01 * AV);        // Cyclin
aM_init = floor(0.01 * AV);       // CDC-2 Kinase (active)
aX_init = floor(0.01 * AV);       // Cyclin Protease (active)
iM_init = floor(0.99 * AV);       // CDC-2 Kinase (inactive)
iX_init = floor(0.99 * AV);       // Cyclin Protease (inactive)


// Unscaled since not clear how to modify rates
// Functional rates

kineticLawOf createC  : cell * vi * AV;
kineticLawOf degC     : cell * kd * C;
kineticLawOf degCtrgX : cell * vd * C * aX / (C + (Kd * AV));
kineticLawOf actM     : cell * (VM1 * AV) * iM * C
                           / ((C + (Kc * AV)) * (iM + (K1 * AV)));
kineticLawOf deactM   : cell * (V2 * AV) * aM / (aM + (K2 * AV));
kineticLawOf actX     : cell * VM3 * aM * iX / (iX + (K3 * AV));
kineticLawOf deactX   : cell * (V4 * AV) * aX / (aX + (K4 * AV));


// Species

 C = createC >> + degC     << + degCtrgX  << + actM (.);
aM = actM    >> + deactM   << + actX (.);
aX = actX    >> + deactX   << + degCtrgX (.) ;
iM = actM    << + deactM   >> ;
iX = actX    << + deactX   >> ;


// System

   C  [C_init]
<*> aM [aM_init]
<*> aX [aX_init]
<*> iM [iM_init]
<*> iX [iX_init]
```

Recent research: hybrid modelling

- stochastic HYPE: stochastic hybrid process algebra

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- map Bio-PEPA model to stochastic HYPE model
  - combine stochastic and deterministic elements
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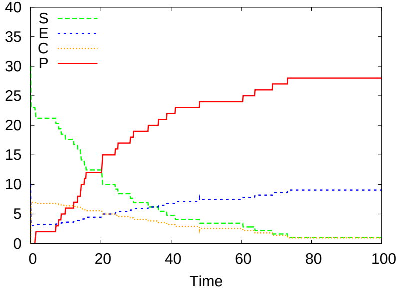
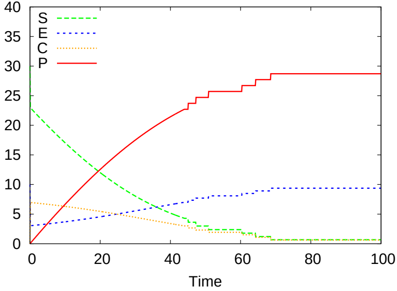
  - provide framework for modelling in stochastic HYPE
- provides benefits of both stochastic simulation and deterministic simulation
- requires specification of thresholds to determine switching of reaction simulation

Deterministic and stochastic simulation

trace: γ slow



trace: low quantities of C



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Src trafficking

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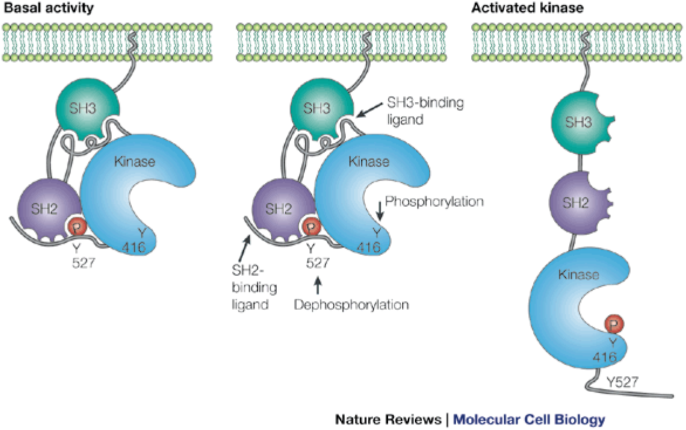
- in either inactive or active configuration

Src protein: inactive and active



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

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- endosomes: membrane-bound compartments within cells
- move along microfilaments or microtubules in one direction

Mechanisms

- experimental research from the Frame laboratory has shown

After stimulation with FGF, Src is found in endosomes throughout the cytoplasm. There is a gradient of inactive Src to active Src from perinuclear region to membrane. Src activation takes place in endosomes. (Sandilands *et al*, 2004)

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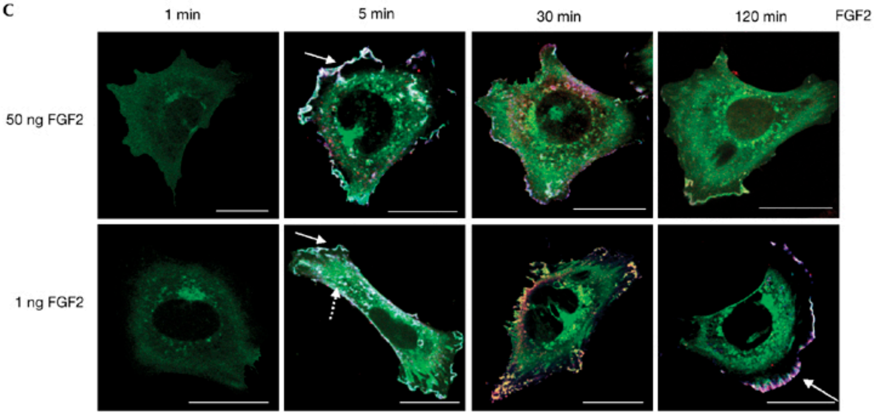
The persistence of active Src at the membrane is inversely related to the quantity of FGF added. (Sandilands *et al*, 2007)

Mechanisms: persistence of response to FGF



(Sandilands *et al*, EMBO Reports 8, 2007)

Modelling protein trafficking

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  - dynamic: behaviour over time, addition of FGF
  - spatial: movement of molecules, endosomes

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  - concrete enough and abstract enough
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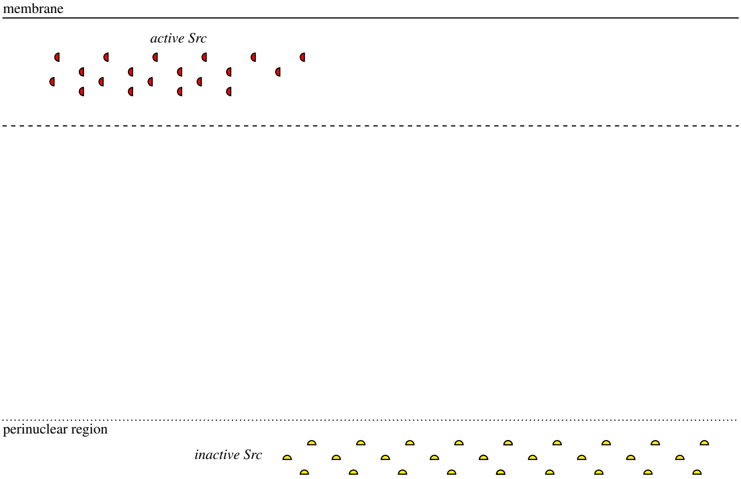
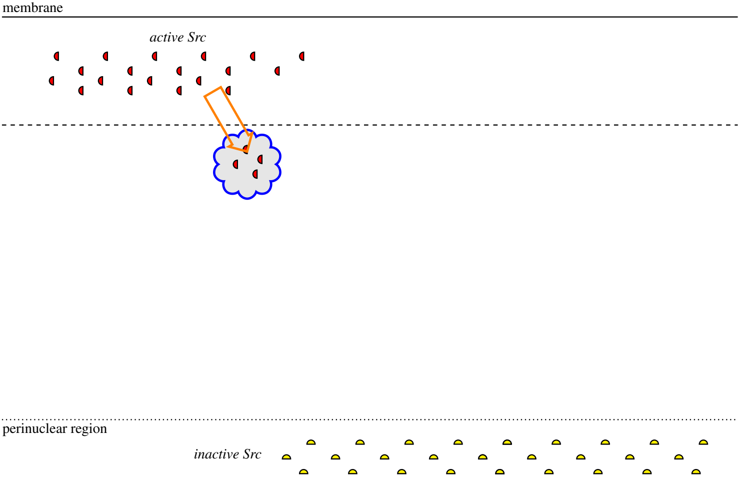
- data
  - qualitative: gradient, recycling loops
  - quantitative: response to addition, endosome data


membrane
active Src
perinuclear region
inactive Src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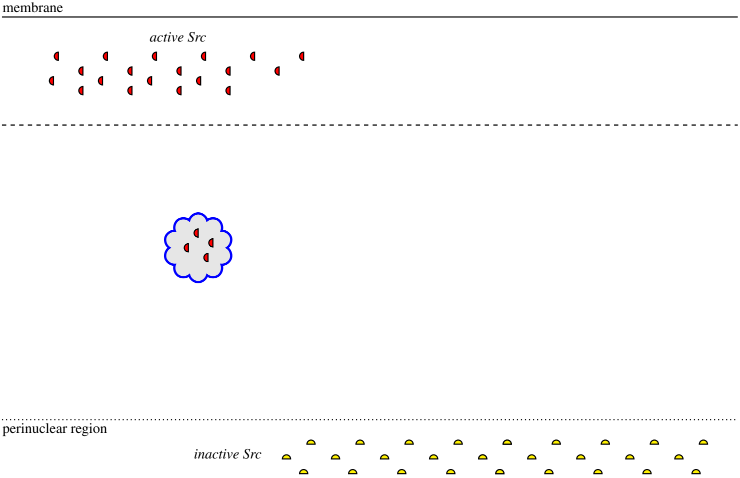
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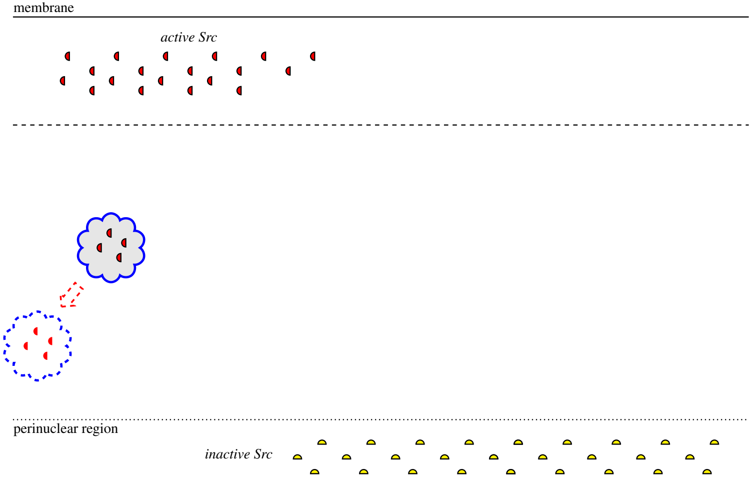
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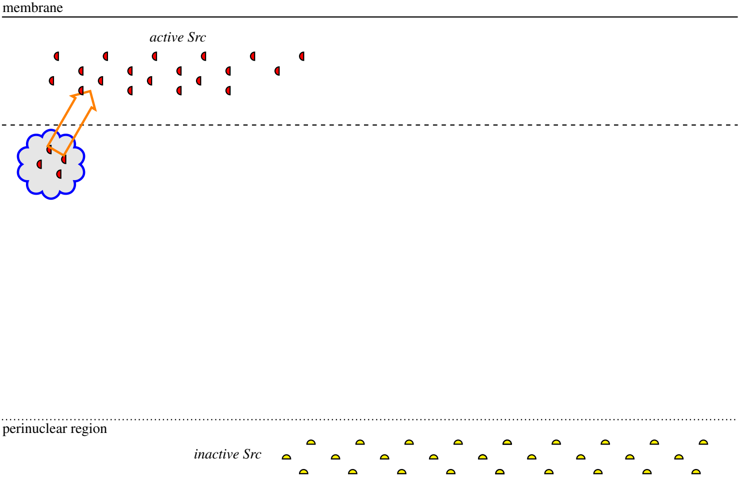
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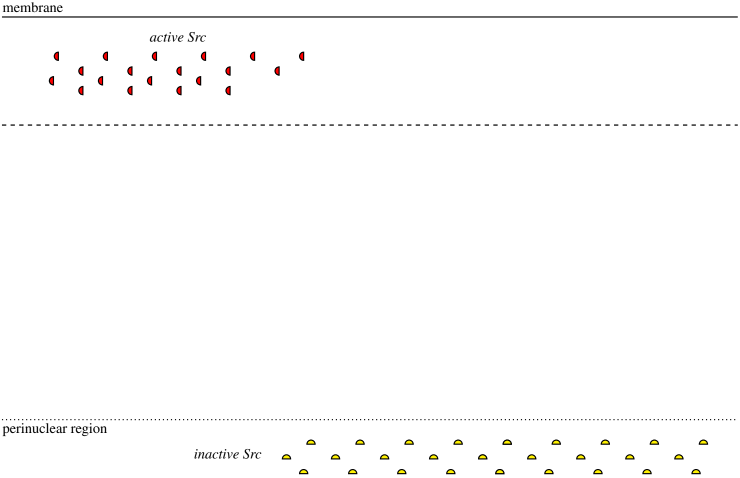
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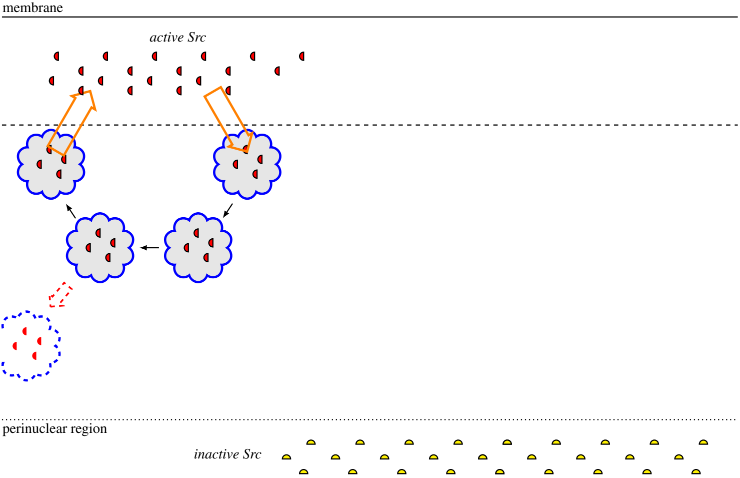
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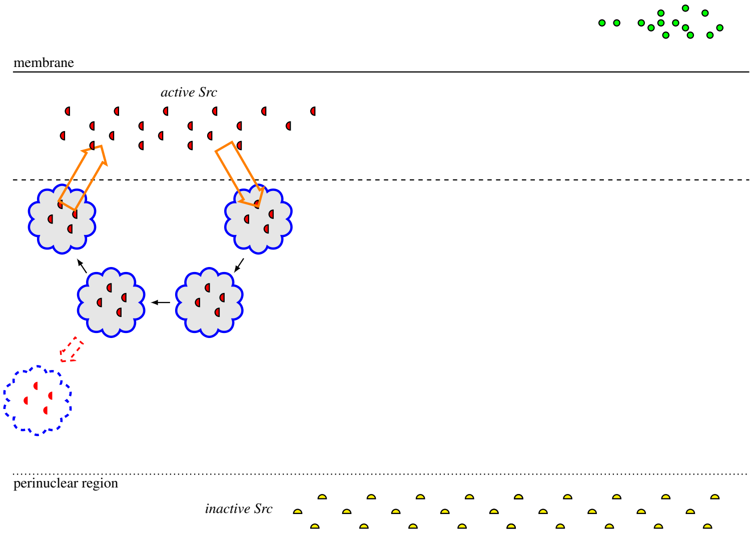
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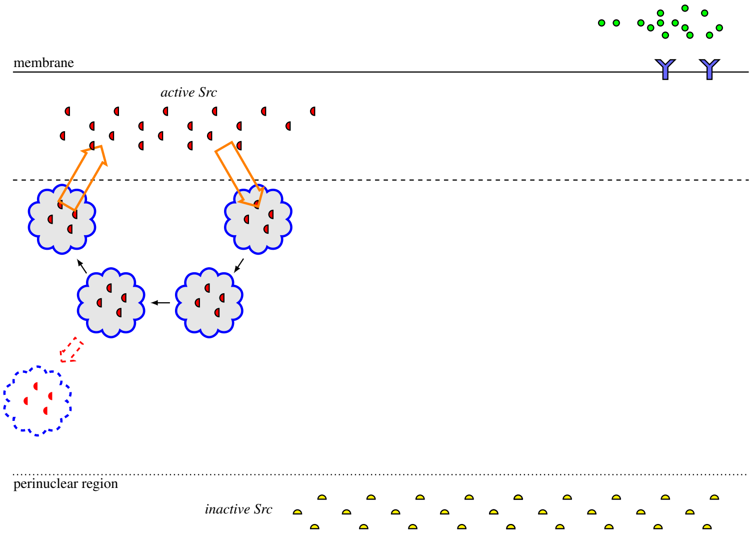
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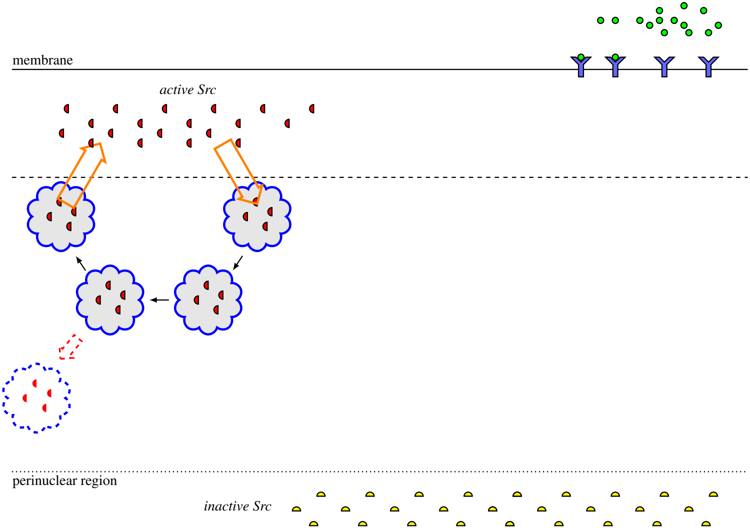
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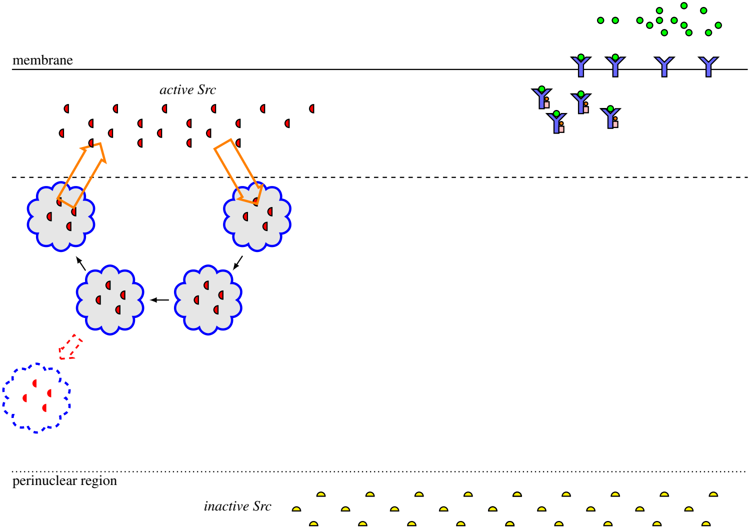
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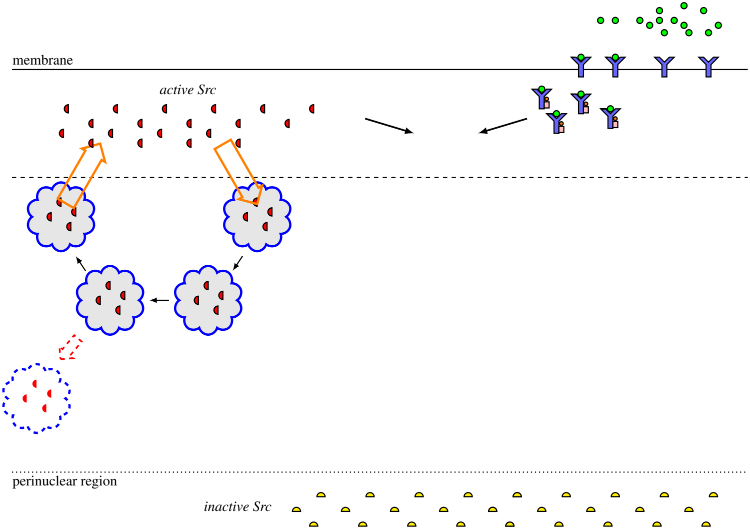
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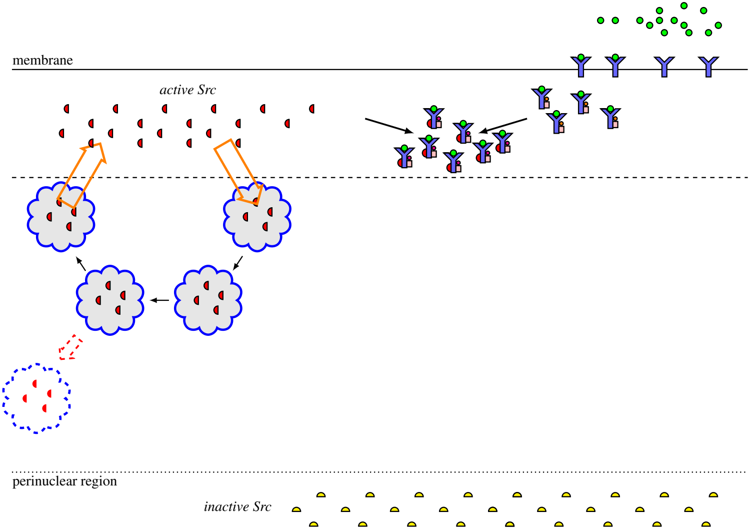
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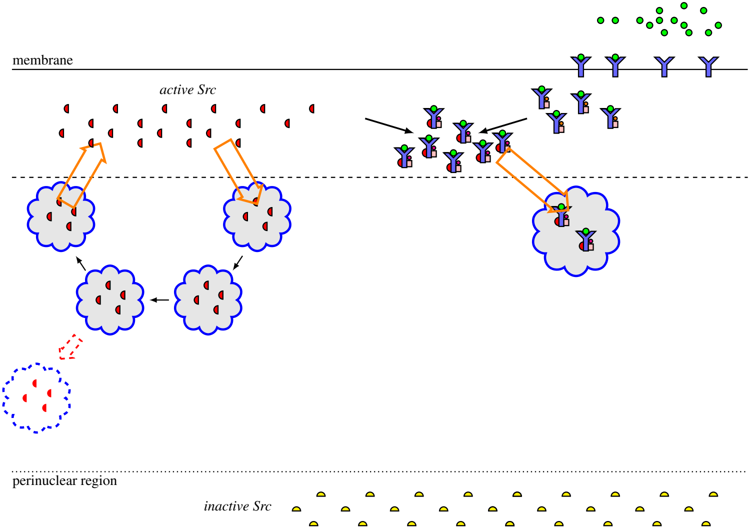
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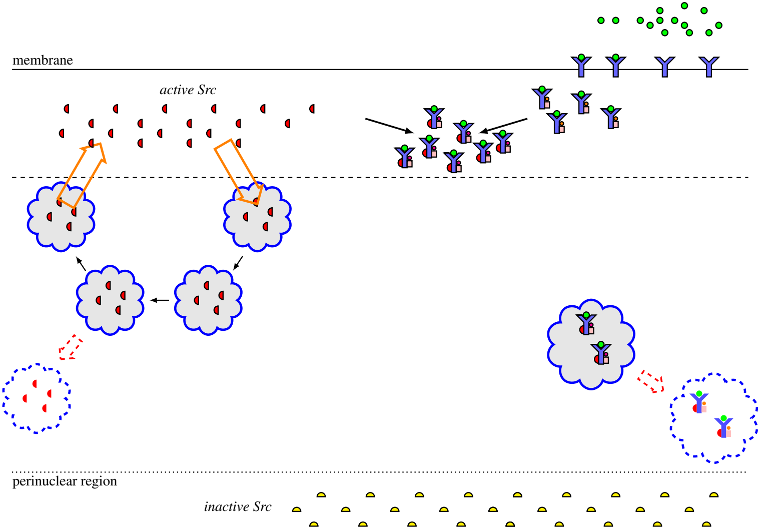
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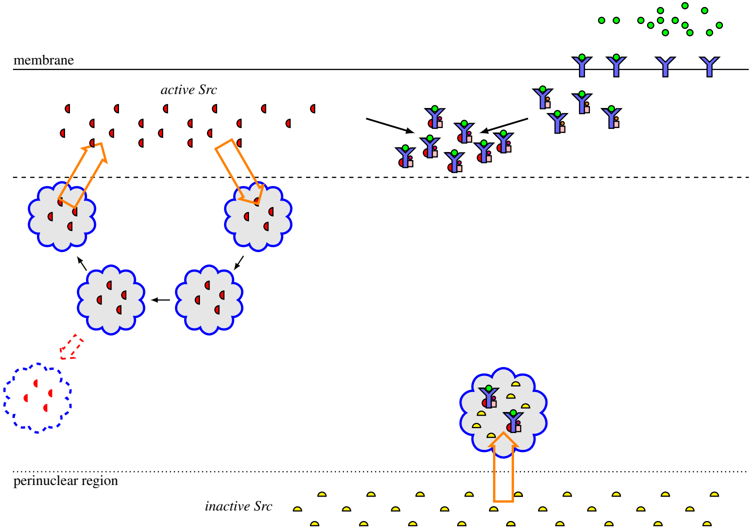
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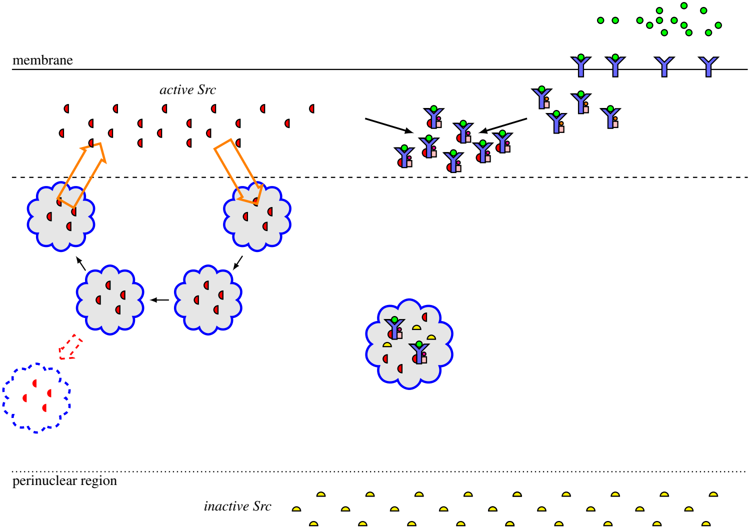
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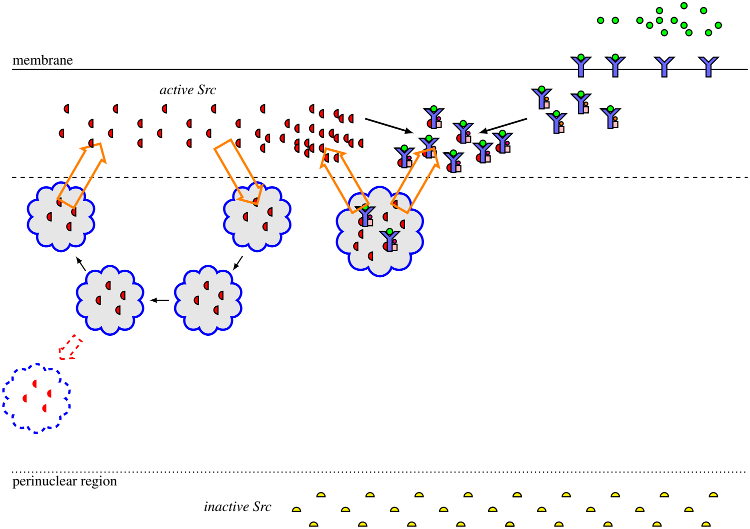
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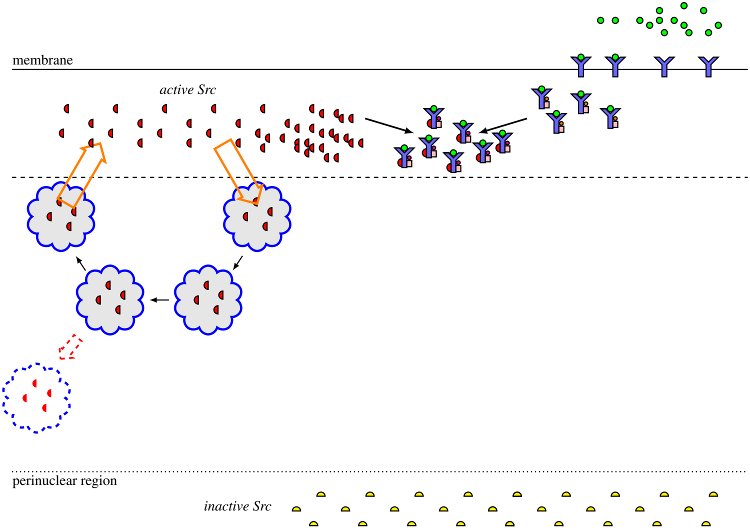
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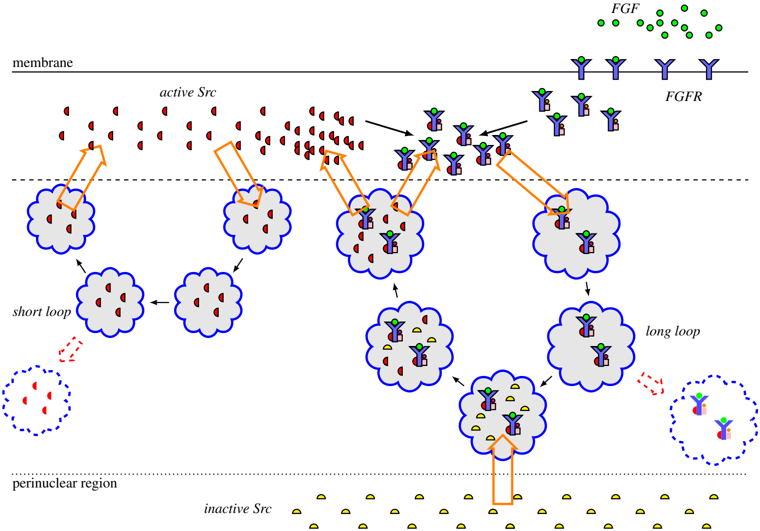
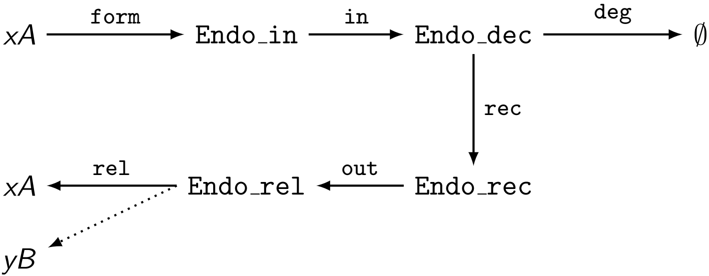
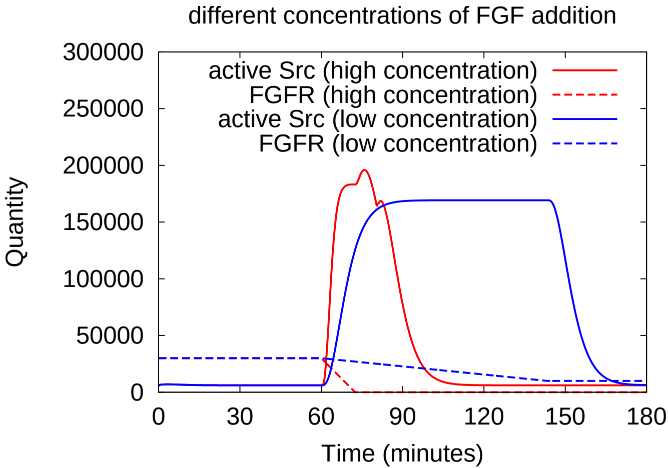

FGF
membrane
FGFR
active Src
short loop
long loop
perinuclear region
inactive Src

Generic recycling loop

- modelling of endosome trafficking



Two loop trafficking model – results



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- fast-slow bisimulation, qualitative
  - based on quasi-steady-state assumption (QSSA), identifies species to be abstracted

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- Bio-PEPA can be applied to complex examples with limited data

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PEPA Group
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Thank you