Modelling protein trafficking: progress and challenges

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Outline

Protein Trafficking

Modelling Biology

Process Algebras

Bio-PEPA

HYPE

Conclusions
Src protein

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

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- in either inactive or active configuration
**Src protein: inactive and active**

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- location in normal cell without growth factor (FGF) addition
  - lots of inactive Src in perinuclear region
  - much less active Src on membrane
- added FGF binds with FGF receptor (FGFR) which becomes active and binds with active Src
- location in normal cell after FGF addition
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- how does this happen?
Endosomes

- endosomes: membrane-bound compartments within cells
- endocytosis: engulfing of molecules by vesicles on the inner side of the membrane, which then merge with endosomes
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- role is to sort molecules either for recycling or degradation
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- vary in contents rather than number or speed
Mechanisms

- experimental research from the Frame laboratory has shown...
Mechanisms

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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)
Mechanisms: gradient from inactive to active

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

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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)
Mechanisms

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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

(Sandilands et al, Nature Cell Biology 14, 2012)
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 protein trafficking

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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
Experimental data
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- qualitative: gradient of activity
- quantitative: persistence of response
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- data from general literature
  - endosomes move along microfilaments and microtubules
  - they move in one direction (mostly)
  - they can move at $1 \mu m/s$
  - cells have diameters of between $10 \mu m$ and $100 \mu m$
Experimental data

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  - endosomes move along microfilaments and microtubules
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  - they can move at $1\mu m/s$
  - 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)
  - Hillston developed ODE interpretation of PEPA (2005)
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- Bio-PEPA, a biological process algebra
  - developed by Ciocchetta and Hillston
  - close match between modelling artificial and natural systems
  - extension of PEPA, functional rates and stoichiometry
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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
  - stochastic hybrid process algebra: piecewise determinsitic Markov processes
Process algebras (continued)

- what is a process algebra?
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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

\[ S @ L \overset{\text{def}}{=} (\alpha_1, \kappa_1) \text{op}_1 S @ L + \ldots + (\alpha_n, \kappa_n) \text{op}_n S @ L \]

where \( \text{op}_i \in \{ \downarrow, \uparrow, \oplus, \ominus, \odot \} \)
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where \( \circ_i \in \{\downarrow, \uparrow, \oplus, \ominus, \odot\} \)

- model: quantities of species, interaction between species

\[
P \overset{\text{def}}{=} S_1@L_1(x_1) \boxtimes \ldots \boxtimes S_p@L_p(x_p)
\]
Bio-PEPA syntax

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\[ P \overset{\text{def}}{=} S_1@L_1(x_1) \otimes \ldots \otimes S_p@L_p(x_p) \]

- system: includes other information required for modelling
  - \( \mathcal{L} \) compartments and locations, dimensionality, sizes
  - \( \mathcal{N} \) species quantities, minimums, maximums, step size
  - \( \mathcal{K} \) parameter definitions
  - \( \mathcal{F} \) functional rates for reactions, definition of \( f_\alpha \)
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\[ S@L \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ_{\text{op}_1} S@L + \ldots + (\alpha_n, \kappa_n) \circ_{\text{op}_n} S@L \]

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  - \( \mathcal{N} \) species quantities, minimums, maximums, step size
  - \( \mathcal{K} \) parameter definitions
  - \( \mathcal{F} \) functional rates for reactions, definition of \( f_{\alpha} \)

- **process-as-species** rather than process-as-molecules
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$

- Prefix rules

$$(((\alpha, \kappa) \downarrow S@L)(\ell) \xrightarrow{(\alpha, [S@L: \downarrow(\ell, \kappa)])} c S@L(\ell - \kappa) \quad \kappa \leq \ell \leq N_{S@L}$$

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

$$(((\alpha, \kappa) \oplus S@L)(\ell) \xrightarrow{(\alpha, [S@L: \oplus(\ell, \kappa)])} c S@L(\ell) \quad \kappa \leq \ell \leq N_{S@L}$$

$$(((\alpha, \kappa) \ominus S@L)(\ell) \xrightarrow{(\alpha, [S@L: \ominus(\ell, \kappa)])} c S@L(\ell) \quad 0 \leq \ell \leq N_{S@L}$$

$$(((\alpha, \kappa) \oslash S@L)(\ell) \xrightarrow{(\alpha, [S@L: \oslash(\ell, \kappa)])} c S@L(\ell) \quad 0 \leq \ell \leq N_{S@L}$$
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((\alpha, \kappa) \downarrow S@L)(\ell) \xrightarrow{\alpha,[S@L:\downarrow(\ell,\kappa)]} S@L(\ell - \kappa) \quad \kappa \leq \ell \leq N_{S@L}
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\[
((\alpha, \kappa) \odot S@L)(\ell) \xrightarrow{\alpha,[S@L:\odot(\ell,\kappa)]} S@L(\ell) \quad 0 \leq \ell \leq N_{S@L}
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$(((\alpha, \kappa) \otimes S@L)(\ell), (\alpha, \kappa)[S@L:\otimes(\ell, \kappa)]) \rightarrow_c S@L(\ell)$ $0 \leq \ell \leq N_{S@L}$
Bio-PEPA semantics (continued)

 Cooperative for $\alpha \in M$

\[
P \xrightarrow{(\alpha,v)}_c P' \quad Q \xrightarrow{(\alpha,u)}_c Q'\]

\[
P \otimes_M Q \xrightarrow{(\alpha,v::u)}_c P' \otimes_M Q'
\] $\alpha \in M$
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in M$

\[
\begin{align*}
  P \xrightarrow{c} (\alpha, v) P' & \quad Q \xrightarrow{c} (\alpha, u) Q' \\
  P \bowtie M Q \xrightarrow{c} (\alpha, v::u) \bowtie M P' & \quad Q' \\
  \alpha \in M
\end{align*}
\]

- Operational semantics for stochastic relation $\rightarrow_s$

\[
\begin{align*}
  P \xrightarrow{c} (\alpha, v) P' \\
  \langle V, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P \rangle \xrightarrow{(\alpha, f_\alpha(v, V, N, K)/h)} \rightarrow_s \langle V, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P' \rangle
\end{align*}
\]
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in M$

$$
\begin{align*}
P \xrightarrow{(\alpha,v)}_c P' & \quad Q \xrightarrow{(\alpha,u)}_c Q' \\
\hat{P} \boxdot_M Q \xrightarrow{(\alpha,v::u)}_c \hat{P'} \boxdot_M Q'
\end{align*}
$$

- operational semantics for stochastic relation $\rightarrow_s$

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

- rate function $f_\alpha$ 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
Modelling with Bio-PEPA

- modelled gradient successfully without cycle
Modelling with Bio-PEPA

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- added gradient into model of trafficking with a combined loop
  - gradient component seemed to make model insensitive to changes
  - very difficult to work with, too many parameters
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- next: combined loop model with abstract gradient
Src trafficking: combined loop model

FGF

membrane

\(aSrc\)

FGFR

\(aFGFR\)

Perinuclear region

\(Src\)

\(20\) seconds

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Modelling protein trafficking: progress and challenges

Biology + Computing = ??
Modelling progress with Bio-PEPA

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Combined loop trafficking model – results
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  - unnecessary to assume a combined loop for both behaviours
  - found out about short and long recycling loops
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  - unnecessary to assume a combined loop for both behaviours
  - found out about short and long recycling loops
- current: two loop model
  - one short, one long
Src trafficking: two loop model

membrane

FGF

FGFR

aSrc

FGFR

aFGFR

Src

aSrc

Src

10 seconds

20 seconds

perinuclear region

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Modelling protein trafficking: progress and challenges

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Two loop trafficking model – results

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Modelling protein trafficking: progress and challenges
Bio-PEPA Eclipse Plug-in

- software tool for Bio-PEPA modelling
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- software tool for Bio-PEPA modelling
- 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)

Available for download at www.biopepa.org
Case studies, publications, manuals
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Bio-PEPA Eclipse Plug-in (continued)
Simplified Bio-PEPA model

active Src at membrane

\[
asrc@mb &= (\text{bind}, 1) \leq asrc@mb + (\text{out}\_sh, 150) \leq asrc@mb + (\text{in}\_sh, 75) \geq asrc@mb + (\text{in}\_long, 100) \geq asrc@mb;
\]
Simplified Bio-PEPA model

- active Src at membrane

\[
\text{aSrc}@mb = (\text{bind},1) \ll a\text{Src}@mb + (\text{out}_\text{sh},150) \ll a\text{Src}@mb + (\text{in}_\text{sh},75) \gg a\text{Src}@mb + (\text{in}_\text{long},100) \gg a\text{Src}@mb;
\]

- endosome in short recycling loop

\[
\text{Endo}_\text{short}@\text{cyto} = (\text{out}_\text{sh},1) \gg \text{Endo}_\text{short}@\text{cyto} + (\text{in}_\text{sh},1) \ll \text{Endo}_\text{short}@\text{cyto} + \ldots ;
\]
Simplified Bio-PEPA model

▶ active Src at membrane

\[ a_{\text{Src@mb}} = (\text{bind,1}) \ll a_{\text{Src@mb}} + (\text{out\_sh,150}) \ll a_{\text{Src@mb}} + (\text{in\_sh,75}) \gg a_{\text{Src@mb}} + (\text{in\_long,100}) \gg a_{\text{Src@mb}}; \]

▶ endosome in short recycling loop

\[ \text{Endo\_short@cyto} = (\text{out\_sh,1}) \gg \text{Endo\_short@cyto} + (\text{in\_sh,1}) \ll \text{Endo\_short@cyto} + \ldots ; \]

▶ model:

\[ a_{\text{Src@mb}}[\text{initial\_aSrc\_mb}] \leftrightarrow \text{Endo\_short@cyto}[\text{initial\_Endo\_short}] \]
Simplified Bio-PEPA model

▸ active Src at membrane

\[
aSrc_{@mb} = (\text{bind},1) \ltimes aSrc_{@mb} + (\text{out\_sh},150) \ltimes aSrc_{@mb} + (\text{in\_sh},75) \rhd aSrc_{@mb} + (\text{in\_long},100) \rhd aSrc_{@mb};
\]

▸ endosome in short recycling loop

\[
\text{Endo\_short}_{@cyto} = (\text{out\_sh},1) \rhd \text{Endo\_short}_{@cyto} + (\text{in\_sh},1) \ltimes \text{Endo\_short}_{@cyto} + \ldots;
\]

▸ model:

\[
aSrc_{@mb}[\text{initial\_aSrc\_mb}] \ltimes \rtimes \text{Endo\_short}_{@cyto}[\text{initial\_Endo\_short}]
\]

▸ reactions

\[
\text{out\_sh}: \quad 150 \quad \text{aSrc} \quad \rightarrow \quad \text{Endo\_short}
\]
\[
\text{in\_sh}: \quad \text{Endo\_short} \quad \rightarrow \quad 75 \quad \text{aSrc}
\]
Stochastic HYPE
Stochastic HYPE

subcomponents

\((C_1(\mathcal{V}) \bowtie \cdots \bowtie C_n(\mathcal{V}))\)
Stochastic HYPE

subcomponents

\( (C_1(V) \bowtie \cdots \bowtie C_n(V)) \bowtie \)

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Stochastic HYPE

\[
\text{subcomponents} \quad \left( C_1(V) \otimes \cdots \otimes C_n(V) \right) \\
\text{controllers} \quad \left( Con_1 \otimes \cdots \otimes Con_m \right)
\]
Stochastic HYPE

subcomponents
\((C_1(V) \circledast \cdots \circledast C_n(V))\)

controllers
\((Con_1 \circledast \cdots \circledast Con_m)\)

well-defined subcomponent
\[ C(V) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(V) + \text{init} : \alpha \cdot C(V) \]
Stochastic HYPE

subcomponents \( (C_1(V) \otimes \cdots \otimes C_n(V)) \)

controllers \( (Con_1 \otimes \cdots \otimes Con_m) \)

well-defined subcomponent

\[
C(V) \overset{def}{=} \sum_{j} a_j : \alpha_j \cdot C(V) + \text{init} : \alpha \cdot C(V)
\]

subcomponents are parameterised by variables
Stochastic HYPE

subcomponents

\[
(\mathcal{C}_1(\mathcal{V}) \otimes \cdots \otimes \mathcal{C}_n(\mathcal{V})) \otimes (\mathcal{Con}_1 \otimes \cdots \otimes \mathcal{Con}_m)
\]

controllers

well-defined subcomponent

\[
\mathcal{C}(\mathcal{V}) \overset{\text{def}}{=} \sum_j \alpha_j : \mathcal{C}(\mathcal{V}) + \text{init} : \alpha \cdot \mathcal{C}(\mathcal{V})
\]
Stochastic HYPE

subcomponents

\[(C_1(\mathcal{V}) \circ \cdot \circ C_n(\mathcal{V})) \circ \cdot \circ (Con_1 \circ \cdot \circ Con_m)\]

controllers

well-defined subcomponent

\[C(\mathcal{V}) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(\mathcal{V}) + \text{init} : \alpha \cdot C(\mathcal{V})\]

events have event conditions: guards and resets
Stochastic HYPE

subcomponents

\[(C_1(\mathcal{V}) \bowtie \cdots \bowtie C_n(\mathcal{V})) \bowtie (Con_1 \bowtie \cdots \bowtie Con_m)\]

controllers

well-defined subcomponent

\[C(\mathcal{V}) \overset{\text{def}}{=} \sum_j a_j : \alpha_j . C(\mathcal{V}) + \text{init} : \alpha . C(\mathcal{V})\]

events have event conditions: guards and resets

\[ec(a_j) = (f(\mathcal{V}), \mathcal{V} = f'(\mathcal{V}))\] discrete events
Stochastic HYPE

subcomponents
\[(C_1(\mathcal{V}) \Join \cdots \Join C_n(\mathcal{V})) \Join (Con_1 \Join \cdots \Join Con_m)\]

controllers

well-defined subcomponent
\[C(\mathcal{V}) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(\mathcal{V}) + \text{init} : \alpha \cdot C(\mathcal{V})\]

events have event conditions: guards and resets
\[ec(a_j) = (f(\mathcal{V}), \mathcal{V}' = f'(\mathcal{V}))\] discrete events
\[ec(\overline{a}_j) = (r, \mathcal{V}' = f'(\mathcal{V}))\] stochastic events
Stochastic HYPE

subcomponents  controllers

\((C_1(V) \Join \cdots \Join C_n(V)) \Join (Con_1 \Join \cdots \Join Con_m)\)

well-defined subcomponent

\[ C(V) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(V) + \text{init} : \alpha \cdot C(V) \]
Stochastic HYPE

subcomponents controllers
\((C_1(V) \circ \cdots \circ C_n(V)) \circ (Con_1 \circ \cdots \circ Con_m)\)

well-defined subcomponent
\[ C(V) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(V) + \text{init} : \alpha \cdot C(V) \]

influences are defined by a triple
Stochastic HYPE

subcomponents

\((C_1(\mathcal{V}) \otimes \cdots \otimes C_n(\mathcal{V}))\) \quad \otimes \quad \text{controllers} \quad (Con_1 \otimes \cdots \otimes Con_m)

well-defined subcomponent

\(C(\mathcal{V}) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(\mathcal{V}) + \text{init} : \alpha \cdot C(\mathcal{V})\)

influences are defined by a triple

\(\alpha_j = (\iota_j, r_j, I(\mathcal{V}))\)
**Stochastic HYPE**

subcomponents

\[(C_1(\mathcal{V}) \circ \ldots \circ C_n(\mathcal{V})) \circ \ldots \circ (Con_1 \circ \ldots \circ Con_m)\]

controllers

well-defined subcomponent

\[C(\mathcal{V}) \overset{\text{def}}{=} \sum_j a_j : \alpha_j \cdot C(\mathcal{V}) + \text{init} : \alpha \cdot C(\mathcal{V})\]

influences are defined by a triple

\[\alpha_j = (\iota_j, r_j, I(\mathcal{V}))\]

influence names are mapped to variables

\[iv(\iota_j) \in \mathcal{V}\]
Stochastic HYPE

subcomponents

\((C_1(V) \bowtie \cdots \bowtie C_n(V)) \bowtie (Con_1 \bowtie \cdots \bowtie Con_m)\)
Stochastic HYPE

subcomponents

\((C_1(V) \star \cdots \star C_n(V)) \star \star\)

controllers

\((Con_1 \star \cdots \star Con_m)\)
Stochastic HYPE

subcomponents

\( (C_1(V) \text{ } \ast \cdots \ast \text{ } C_n(V)) \)

controllers

\( (Con_1 \text{ } \ast \cdots \ast \text{ } Con_m) \)

controller grammar
Stochastic HYPE

subcomponents

\[ (C_1(V) \bowtie \cdots \bowtie C_n(V)) \bowtie (Con_1 \bowtie \cdots \bowtie Con_m) \]

controller grammar

\[ M ::= a.M \mid 0 \mid M + M \]
Stochastic HYPE

subcomponents

\( (C_1(V) \otimes \cdots \otimes C_n(V)) \)

controllers

\( (Con_1 \otimes \cdots \otimes Con_m) \)

can

ccontroller grammer

\[ M ::= a.M \mid 0 \mid M + M \]
Stochastic HYPE

subcomponents

\((C_1(V) \And \cdots \And C_n(V))\) \And \(\ldots\) \And \(\ldots\) \And \(C_n(V)\)

controllers

\(\ldots\) \And \(\ldots\) \And \(\ldots\) \And \(C_n(V)\)

controller grammar

\[M ::= a.M \mid 0 \mid M + M\]

\[Con ::= M \mid Con \And Con\]
Stochastic HYPE applied to biology

- a model has $n$ variables defined over $\mathbb{R}$: species quantities
Stochastic HYPE applied to biology

- a model has \( n \) variables defined over \( \mathbb{R} \): species quantities
- each subcomponent represents flows affecting a variable: production, binding, activation, degradation, removal
Stochastic HYPE applied to biology

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Stochastic HYPE applied to biology

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Stochastic HYPE applied to biology

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- each influence represents a specific flow: degradation
- each controller represents sequencing of events: day/night cycle
- each discrete event represents something happening instantaneously when a condition becomes true, with a possible change of values: addition of growth factor
- 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
Stochastic HYPE modelling

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- major differences from Bio-PEPA
  - HYPE allows coordinate model of space rather than explicit abstract locations
  - HYPE allows continuous and stochastic behaviour together
  - likely to be valuable when small quantities of some species
Stochastic HYPE modelling

- output of model is a trajectory consisting of
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- major differences from Bio-PEPA
  - HYPE allows coordinate model of space rather than explicit abstract locations
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- application to protein trafficking
  - work in progress
  - SimHyA simulator
The Repressilator

- synthetic network
The Repressilator

- synthetic network
- three genes with three inhibitors
The Repressilator

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The Repressilator

➤ synthetic network

➤ three genes with three inhibitors

➤ reporter of green fluorescent protein (GFP)

➤ negative feedback cycle
  ➤ each gene produces a protein
  ➤ protein inhibits transcription of mRNA by another gene
  ➤ other gene cannot produce its protein
The Repressilator

- synthetic network
- three genes with three inhibitors
- reporter of green fluorescent protein (GFP)
- negative feedback cycle
  - each gene produces a protein
  - protein inhibits transcription of mRNA by another gene
  - 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

\[ \text{Gene}_A \xrightarrow{\text{trs}_A} \text{mRNA}_A \]
The Repressilator

\[ \text{Gene}_A \xrightarrow{\text{trs}_A} \text{mRNA}_A \xrightarrow{\text{dm}_A} \text{Gene}_B \xrightarrow{\text{trs}_B} \text{mRNA}_B \xrightarrow{\text{dm}_B} \text{Gene}_C \xrightarrow{\text{trs}_C} \text{mRNA}_C \xrightarrow{\text{dm}_C} \]
The Repressilator

\[ \text{Gene}_A \xrightarrow{\text{trs}_A} \text{mRNA}_A \xrightarrow{\text{trl}_A} \text{Pr}_A \]

\[ \downarrow \text{dm}_A \]

Vashti Galpin

Modelling protein trafficking: progress and challenges
The Repressilator

\[ \text{Gene}_A \xrightarrow{\text{trs}_A} \text{mRNA}_A \xrightarrow{\text{trl}_A} \text{Pr}_A \]

\[ \downarrow \text{dm}_A \quad \downarrow \text{dp}_A \]
The Repressilator

\[ Gene_A \xrightarrow{trs_A} mRNA_A \xrightarrow{trl_A} Pr_A \]
\[ \downarrow dm_A \quad \downarrow dp_A \]

\[ Gene_B \xrightarrow{trs_B} mRNA_B \xrightarrow{trl_B} Pr_B \]
\[ \downarrow dm_B \quad \downarrow dp_B \]
The Repressilator

\[ \text{Gene}_A \xrightarrow{\text{trs}_A} \text{mRNA}_A \xrightarrow{\text{trl}_A} \text{Pr}_A \]
\[ \downarrow \text{dm}_A \quad \downarrow \text{dp}_A \]

\[ \text{Gene}_B \xrightarrow{\text{trs}_B} \text{mRNA}_B \xrightarrow{\text{trl}_B} \text{Pr}_B \]
\[ \downarrow \text{dm}_B \quad \downarrow \text{dp}_B \]

\[ \text{Gene}_C \xrightarrow{\text{trs}_C} \text{mRNA}_C \xrightarrow{\text{trl}_C} \text{Pr}_C \]
\[ \downarrow \text{dm}_C \quad \downarrow \text{dp}_C \]
The Repressilator

Gene_A →^{trs_A} mRNA_A →^{trl_A} Pr_A
↓^{dm_A} \hspace{1cm} \downarrow^{dp_A}

Gene_B →^{trs_B} mRNA_B →^{trl_B} Pr_B
↓^{dm_B} \hspace{1cm} \downarrow^{dp_B}

Gene_C →^{trs_C} mRNA_C →^{trl_C} Pr_C
↓^{dm_C} \hspace{1cm} \downarrow^{dp_C}
The Repressilator

Gene_A $\xrightarrow{trs_A} mRNA_A \xrightarrow{trl_A} Pr_A$
$\downarrow dm_A \downarrow dp_A$

Gene_B $\xrightarrow{trs_B} mRNA_B \xrightarrow{trl_B} Pr_B$
$\downarrow dm_B \downarrow dp_B$

Gene_C $\xrightarrow{trs_C} mRNA_C \xrightarrow{trl_C} Pr_C$
$\downarrow dm_C \downarrow dp_C$
The Repressilator

Gene_A \xrightarrow{trs_A} mRNA_A \xrightarrow{trl_A} Pr_A
\downarrow dm_A \downarrow dp_A

Gene_B \xrightarrow{trs_B} mRNA_B \xrightarrow{trl_B} Pr_B
\downarrow dm_B \downarrow dp_B

Gene_C \xrightarrow{trs_C} mRNA_C \xrightarrow{trl_C} Pr_C
\downarrow dm_C \downarrow dp_C

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The Repressilator

\[
\begin{align*}
\text{Gene}_A & \xrightarrow{\text{trs}_A} m\text{RNA}_A & \xrightarrow{\text{trl}_A} Pr_A \\
& \quad \downarrow \text{dm}_A & \quad \downarrow \text{dp}_A \\
\text{Gene}_B & \xrightarrow{\text{trs}_B} m\text{RNA}_B & \xrightarrow{\text{trl}_B} Pr_B \\
& \quad \downarrow \text{dm}_B & \quad \downarrow \text{dp}_B \\
\text{Gene}_C & \xrightarrow{\text{trs}_C} m\text{RNA}_C & \xrightarrow{\text{trl}_C} Pr_C \\
& \quad \downarrow \text{dm}_C & \quad \downarrow \text{dp}_C
\end{align*}
\]
The Repressilator

Gene\(_A\) \(\xrightarrow{k_p} PrA\) \(\xrightarrow{k_d}\)

Gene\(_B\) \(\xrightarrow{k_p} PrB\) \(\xrightarrow{k_d}\)

Gene\(_C\) \(\xrightarrow{k_p} PrC\) \(\xrightarrow{k_d}\)
The Repressilator in HYPE

degradation and production flows for Gene A:

\[ G_A^{dg}(X) \overset{\text{def}}{=} \text{init} : (d_A, -k_d, \text{linear}(X)).G_A^{dg}(X) \]

\[ G_A^{pr} \overset{\text{def}}{=} \text{inhibit}_A : (p_A, 0, \text{const}).G_A^{pr} + \text{express}_A : (p_A, k_p, \text{const}).G_A^{pr} + \text{init} : (p_A, k_p, \text{const}).G_A^{pr} \]
The Repressilator in HYPE

- degradation and production flows for Gene A:

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G_A^{pr} & \overset{\text{def}}{=} \text{inhibit}_A : (p_A, 0, \text{const}).G_A^{pr} \\
+ & \quad \text{express}_A : (p_A, k_p, \text{const}).G_A^{pr} \\
+ & \quad \text{init} : (p_A, k_p, \text{const}).G_A^{pr}
\end{align*}
\]

- composed: \( \textbf{Gene}_A(A) \overset{\text{def}}{=} (G_A^{dg}(A) \boxtimes G_A^{pr}) \)
The Repressilator in HYPE

- degradation and production flows for Gene A:

\[
G_A^{dg}(X) \overset{\text{def}}{=} \text{init} : (d_A, -k_d, \text{linear}(X)) \cdot G_A^{dg}(X)
\]

\[
G_A^{pr} \overset{\text{def}}{=} \text{inhibit}_A : (p_A, 0, \text{const}).G_A^{pr}
\]

+ \text{express}_A : (p_A, k_p, \text{const}).G_A^{pr}

+ \text{init} : (p_A, k_p, \text{const}).G_A^{pr}

- composed: Gene_A(A) \overset{\text{def}}{=} (G_A^{dg}(A) \circledast G_A^{pr})

- “controller”: Con_A \overset{\text{def}}{=} \text{inhibit}_A \cdot \text{express}_A \cdot Con_A
The Repressilator in HYPE

- degradation and production flows for Gene A:
  \[ G_A^{dg}(X) \overset{\text{def}}{=} \text{init} : (d_A, -k_d, \text{linear}(X)).G_A^{dg}(X) \]
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- influences mapped to variables: \( \text{iv}(d_A) = A \quad \text{iv}(p_A) = A \)
The Repressilator in HYPE

- degradation and production flows for Gene A:
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  \[ + \text{express}_A : (p_A, k_p, \text{const}).G^{pr}_A \]
  \[ + \text{init} : (p_A, k_p, \text{const}).G^{pr}_A \]

- composed: \[ \text{Gene}_A(A) \overset{\text{def}}{=} (G^{dg}_A(A) \otimes G^{pr}_A) \]

- “controller”: \[ \text{Con}_A \overset{\text{def}}{=} \text{inhibit}_A.\text{express}_A.\text{Con}_A \]

- influences mapped to variables: \[ \text{iv}(d_A) = A \quad \text{iv}(p_A) = A \]

- event conditions: \[ \text{ec}(\text{inhibit}_A) = (C > p, \text{true}) \]
  \[ \text{ec}(\text{express}_A) = (C \leq p, \text{true}) \]
The Repressilator – protein levels over time

\[(Gene_A(A) \bowtie Gene_B(B) \bowtie Gene_C(C)) \bowtie \text{init.}(Con_A \parallel Con_B \parallel Con_C)\]
The Repressilator – protein levels over time

\((Gene_A(A) \times Gene_B(B) \times Gene_C(C)) \times \text{init.}(Con_A \mid Con_B \mid Con_C)\)

\(k_p = 1.00 \quad k_d = 0.01\)
Conclusions

Biology + Computing = ??
Conclusions

Computing + Biology = ??
Conclusions

Computing + Biology = ??

- 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
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Thank you
Bio-PEPA syntax

- two-level syntax
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \quad \text{op} \quad S \mid S + S \quad \text{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \ op \ S \ | \ S + S \quad \text{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]

- \( \alpha \) action, reaction name, \( \kappa \) stoichiometric coefficient
- \( \uparrow \) product, \( \downarrow \) reactant
- \( \oplus \) activator, \( \ominus \) inhibitor, \( \odot \) generic modifier
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- model component, system

\[ P ::= S(\ell) | P \otimes \ell P \]
Bio-PEPA syntax

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Bio-PEPA syntax

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- model component, system

\[ P ::= S(\ell) \mid P \uplus P \]

- need a more constrained form
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} \left( \alpha_1, \kappa_1 \right) \circ \rho_1 C + \ldots + \left( \alpha_n, \kappa_n \right) \circ \rho_n C \text{ with all } \alpha_i \text{'s distinct} \]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ p_1 C + \ldots + (\alpha_n, \kappa_n) \circ p_n C \]  
with all \( \alpha_i \)'s distinct

\[ P \overset{\text{def}}{=} C_1(\ell_1) \triangleleft \ldots \triangleleft \triangleleft C_m(\ell_m) \]  
with all \( C_i \)'s distinct

\[ P = \langle V, N, K, F, \text{Comp}, P \rangle \]  
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
Well-defined Bio-PEPA systems

▪ well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1 \circ p_1 C + \ldots + (\alpha_n, \kappa_n \circ p_n C \text{ with all } \alpha_i \text{'s distinct}}\]

▪ well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \bigotimes_{L_1} \ldots \bigotimes_{L_{m-1}} C_m(\ell_m) \text{ with all } C_i \text{'s distinct} \]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1)_{o p_1} C + \ldots + (\alpha_n, \kappa_n)_{o p_n} C \] with all \( \alpha_i \)'s distinct

- well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \bigotimes \ldots \bigotimes C_m(\ell_m) \] with all \( C_i \)'s distinct
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species
  \[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ_p 1 C + \ldots + (\alpha_n, \kappa_n) \circ_p n C \] with all \( \alpha_i \)'s distinct

- well-defined Bio-PEPA model
  \[ P \overset{\text{def}}{=} C_1(\ell_1) \otimes_1 \ldots \otimes_{m-1} C_m(\ell_m) \] with all \( C_i \)'s distinct

- well-defined Bio-PEPA system
  \[ \mathcal{P} = \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P \rangle \]
Well-defined Bio-PEPA systems

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\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ C + \ldots + (\alpha_n, \kappa_n) \circ C \] with all \( \alpha_i \)'s distinct

- well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \triangleleft \ldots \triangleleft C_m(\ell_m) \] with all \( C_i \)'s distinct

- well-defined Bio-PEPA system

\[ \mathcal{P} = \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P \rangle \]

- 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

\[ S + E \xleftrightarrow{\text{enzyme}} SE \xrightarrow{\text{reaction}} P + E \]
Example: reaction with enzyme

\[ S + E \xleftrightarrow{} SE \rightarrow P + E \]

\[ S(\ell_S) \otimes E(\ell_E) \otimes SE(\ell_{SE}) \otimes P(\ell_P) \]

where

\[ S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \]
\[ E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \]
\[ SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \]
\[ P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \]
Example: reaction with enzyme

\[ S + E \xleftrightarrow{\text{SE}} \rightarrow P + E \]

\[ S(\ell_S) \boxtimes E(\ell_E) \boxtimes SE(\ell_{SE}) \boxtimes P(\ell_P) \text{ where} \]

\[ S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \]
\[ E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \]
\[ SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \]
\[ P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \]
Example: reaction with enzyme

\[ S + E \xrightarrow{\text{reaction}} SE \xrightarrow{\text{reaction}} P + E \]

\[ S(\ell_S) \bowtie E(\ell_E) \bowtie SE(\ell_{SE}) \bowtie P(\ell_P) \text{ where} \]

\[ S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \]
\[ E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \]
\[ SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \]
\[ P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \]
Example: reaction with enzyme

\[ S + E \xrightarrow{\leftrightarrow} SE \rightarrow P + E \]

\[ S(\ell_S) \bowtie E(\ell_E) \bowtie SE(\ell_{SE}) \bowtie P(\ell_P) \]

where

\[ S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \]
\[ E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \]
\[ SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \]
\[ P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \]
Example: reaction with enzyme

1. $S + E \xrightleftharpoons{} SE \rightarrow P + E$

2. $S(\ell_S) \bowtie E(\ell_E) \bowtie SE(\ell_SE) \bowtie P(\ell_P)$ where

   - $S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S$
   - $E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E$
   - $SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE$
   - $P \overset{\text{def}}{=} (\gamma, 1) \uparrow P$

3. $S \xrightarrow{E} P$
Example: reaction with enzyme

- $S + E \xleftrightarrow{SE} P + E$
  - $S(\ell_S) \star E(\ell_E) \star SE(\ell_{SE}) \star P(\ell_P)$ where

  $S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S$
  $E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E$
  $SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE$
  $P \overset{\text{def}}{=} (\gamma, 1) \uparrow P$

- $S \xrightarrow{E} P$
  - $S'(\ell_S') \star E'(\ell_E') \star P'(\ell_P')$ where
Example: reaction with enzyme

\[ S + E \xleftrightarrow{SE} P + E \]

\[ S(\ell_S) \boxtimes E(\ell_E) \boxtimes SE(\ell_{SE}) \boxtimes P(\ell_P) \text{ where} \]

\[ S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \]
\[ E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \]
\[ SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \]
\[ P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \]

\[ S \xrightarrow{E} P \]

\[ S'(\ell_{S'}) \boxtimes E'(\ell_{E'}) \boxtimes P'(\ell_{P'}) \text{ where} \]

\[ S' \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \quad E' \overset{\text{def}}{=} (\gamma, 1) \oplus E' \quad P' \overset{\text{def}}{=} (\gamma, 1) \uparrow P' \]
Example: reaction with enzyme

➤ $S + E \xleftrightarrow{SE} P + E$

➤ $S(\ell_S) \bowtie E(\ell_E) \bowtie SE(\ell_{SE}) \bowtie P(\ell_P)$ where

\[
S \overset{def}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S
\]

\[
E \overset{def}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E
\]

\[
SE \overset{def}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE
\]

\[
P \overset{def}{=} (\gamma, 1) \uparrow P
\]

➤ $S \xrightarrow{E} P$

➤ $S'(\ell_{S'}) \bowtie E'(\ell_{E'}) \bowtie P'(\ell_{P'})$ where

\[
S' \overset{def}{=} (\gamma, 1) \downarrow S'
\]

\[
E' \overset{def}{=} (\gamma, 1) \oplus E'
\]

\[
P' \overset{def}{=} (\gamma, 1) \uparrow P'
\]
Example: reaction with enzyme

- \( S + E \xleftrightarrow{SE} P + E \)

- \( S(\ell_S) \bowtie E(\ell_E) \bowtie SE(\ell_{SE}) \bowtie P(\ell_P) \) where

  \( S \overset{\text{def}}{=} (\alpha, 1) \downarrow S + (\beta, 1) \uparrow S \)

  \( E \overset{\text{def}}{=} (\alpha, 1) \downarrow E + (\beta, 1) \uparrow E + (\gamma, 1) \uparrow E \)

  \( SE \overset{\text{def}}{=} (\alpha, 1) \uparrow SE + (\beta, 1) \downarrow SE + (\gamma, 1) \downarrow SE \)

  \( P \overset{\text{def}}{=} (\gamma, 1) \uparrow P \)

- \( S \xrightarrow{E} P \)

- \( S'(\ell_{S'}) \bowtie E'(\ell_{E'}) \bowtie P'(\ell_{P'}) \) where

  \( S' \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \)

  \( E' \overset{\text{def}}{=} (\gamma, 1) \oplus E' \)

  \( P' \overset{\text{def}}{=} (\gamma, 1) \uparrow P' \)
Example: reaction with enzyme, max level 3

- state vector \((S, E, SE, P)\) and \(N_S = N_E = N_{SE} = N_P = 3\)
Example: reaction with enzyme, max level 3

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

\[
\begin{align*}
(3,3,0,0) &\xrightarrow{\alpha} (2,2,1,0) &\xrightarrow{\alpha} (1,1,2,0) &\xrightarrow{\alpha} (0,0,3,0) \\
&\downarrow{\beta} &\downarrow{\beta} &\downarrow{\beta} \\
(2,3,0,1) &\xrightarrow{\alpha} (1,2,1,1) &\xrightarrow{\alpha} (0,1,2,1) &\xrightarrow{\gamma} \\
&\downarrow{\beta} &\downarrow{\beta} \downarrow{\beta} \\
(1,3,0,2) &\xrightarrow{\alpha} (0,2,1,2) &\downarrow{\gamma} \\
&\downarrow{\beta} \\
(0,3,0,3) &\downarrow{\gamma}
\end{align*}
\]
Example: reaction with enzyme, max level 7

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

- initial parameters for species representing basal behaviour
  - no decision species, no added FGF, no active FGFR
  - long recycling loop inactive so no species from it
  - hence only 3 species present initially
Parameters

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  - no decision species, no added FGF, no active FGFR
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- rate of entry and probability of recycling in each loop
Parameters

- initial parameters for species representing basal behaviour
  - no decision species, no added FGF, no active FGFR
  - long recycling loop inactive so no species from it
  - hence only 3 species present initially

- rate of entry and probability of recycling in each loop

- input and output stoichiometry for each loop
  - short loop: input and output the same
  - long loop: output much larger than input
Parameters

- initial parameters for species representing basal behaviour
  - no decision species, no added FGF, no active FGFR
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  - hence only 3 species present initially

- rate of entry and probability of recycling in each loop

- 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
Parameters (continued)

- at least 13 unknown parameters – not so simple
- enable short recycling loop only
- find parameters to balance short loop
  - 50% of active Src at membrane
  - 50% of active Src in the short recycling loop
- 6 parameters not yet specified
Parameters (continued)

- at least 13 unknown parameters – not so simple
- enable short recycling loop only
- find parameters to balance short loop
  - 50% of active Src at membrane
  - 50% of active Src in the short recycling loop
- 6 parameters not yet specified
- enable the long recycling loop
- guess some parameters
- enable the doser and see what happens