Fragmenting the early EGFR pathway (solution)

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January 28, 2010

1 The model

We consider the following rule set:

r01: $EGF(r^1)$, $EGFR(l^1,r) \longrightarrow EGF(r)$, $EGFR(l,r)$
r02: $EGF(r)$, $EGFR(l,r) \longrightarrow EGF(r^1)$, $EGFR(l^1,r)$
r03: $EGF(r^2)$, $EGF(r^1)$, $EGFR(l^2,r)$, $EGFR(l^1,r) \longrightarrow EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(l^2,r^1)$
r04: $EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(l^2,r^1) \longrightarrow EGF(r^2)$, $EGF(r^1)$, $EGFR(l^2,r)$, $EGFR(l^1,r)$
r05: $EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(Y68_u,l^2,r^1) \longrightarrow EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(Y68_p,l^2,r^1)$
r06: $EGFR(Y68_p) \longrightarrow EGFR(Y68_u)$
r07: $EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(Y48_u,l^2,r^1) \longrightarrow EGF(r^3)$, $EGF(r^2)$, $EGFR(l^3,r^1)$, $EGFR(Y48_p,l^2,r^1)$
r08: $EGFR(Y48_p) \longrightarrow EGFR(Y48_u)$
r09: $EGFR(Y48^1_p,r^-)$, $SHC(Y7_u,pi^1) \longrightarrow EGFR(Y48^1_p,r^-)$, $SHC(Y7_p,pi^1)$
r10: $SHC(Y7_p,pi^-) \longrightarrow SHC(Y7_u,pi^-)$
r11: $SHC(Y7_p,pi) \longrightarrow SHC(Y7_u,pi)$
r12: $EGFR(Y68_p)$, $GRB2(a,b) \longrightarrow EGFR(Y68^1_p)$, $GRB2(a^1,b)$
r13: $EGFR(Y68^1_p)$, $GRB2(a^1,b) \longrightarrow EGFR(Y68_p)$, $GRB2(a,b)$
r14: $EGFR(Y68_p)$, $GRB2(a,b^-) \longrightarrow EGFR(Y68^1_p)$, $GRB2(a^1,b^-)$
r15: $EGFR(Y68^1_p)$, $GRB2(a^1,b^-) \longrightarrow EGFR(Y68_p)$, $GRB2(a,b^-)$
r16: $EGFR(Y68^1_p)$, $GRB2(a^1,b)$, $SOS(d) \longrightarrow EGFR(Y68^2_p)$, $GRB2(a^2,b^1)$, $SOS(d^1)$
r17: $EGFR(Y68^2_p)$, $GRB2(a^2,b^1)$, $SOS(d^1) \longrightarrow EGFR(Y68^1_p)$, $GRB2(a^1,b)$, $SOS(d)$
r18: $GRB2(a,b)$, $SOS(d) \longrightarrow GRB2(a,b^1)$, $SOS(d^1)$
r19: $GRB2(a,b^1)$, $SOS(d^1) \longrightarrow GRB2(a,b)$, $SOS(d)$
r20: $GRB2(a^1,b)$, $SHC(Y7^1_p,pi)$, $SOS(d) \longrightarrow GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi)$, $SOS(d^1)$
r21: $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi)$, $SOS(d^1) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1_p,pi)$, $SOS(d)$

r22: $GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^-\right), SOS(d) \longrightarrow GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^-\right), SOS\left(d^1\right)$
r23: $GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^-\right), SOS\left(d^1\right) \longrightarrow GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^-\right), SOS(d)$
r24: $EGFR\left(Y48_p\right), SHC(Y7_u,pi) \longrightarrow EGFR\left(Y48^1_p\right), SHC\left(Y7_u,pi^1\right)$
r25: $EGFR\left(Y48^1_p\right), SHC\left(Y7_u,pi^1\right) \longrightarrow EGFR\left(Y48_p\right), SHC(Y7_u,pi)$
r26: $EGFR\left(Y48_p\right), SHC\left(Y7_p,pi\right) \longrightarrow EGFR\left(Y48^1_p\right), SHC\left(Y7_p,pi^1\right)$
r27: $EGFR\left(Y48^1_p\right), SHC\left(Y7_p,pi^1\right) \longrightarrow EGFR\left(Y48_p\right), SHC\left(Y7_p,pi\right)$
r28: $EGFR\left(Y48_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi\right) \longrightarrow EGFR\left(Y48^2_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^2\right)$
r29: $EGFR\left(Y48^2_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^2\right) \longrightarrow EGFR\left(Y48_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi\right)$
r30: $EGFR\left(Y48_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi\right), SOS\left(d^1\right) \longrightarrow EGFR\left(Y48^3_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^3\right), SOS\left(d^1\right)$
r31: $EGFR\left(Y48^3_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^3\right), SOS\left(d^1\right) \longrightarrow EGFR\left(Y48_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi\right), SOS\left(d^1\right)$
r32: $EGFR\left(Y48^1_p\right), GRB2(a,b), SHC\left(Y7_p,pi^1\right) \longrightarrow EGFR\left(Y48^2_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^2\right)$
r33: $EGFR\left(Y48^2_p\right), GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi^2\right) \longrightarrow EGFR\left(Y48^1_p\right), GRB2(a,b), SHC\left(Y7_p,pi^1\right)$
r34: $GRB2(a,b), SHC\left(Y7_p,pi\right) \longrightarrow GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi\right)$
r35: $GRB2\left(a^1,b\right), SHC\left(Y7^1_p,pi\right) \longrightarrow GRB2(a,b), SHC\left(Y7_p,pi\right)$
r36: $GRB2(a,b^-), SHC\left(Y7_p,pi\right) \longrightarrow GRB2\left(a^1,b^-\right), SHC\left(Y7^1_p,pi\right)$
r37: $GRB2\left(a^1,b^-\right), SHC\left(Y7^1_p,pi\right) \longrightarrow GRB2(a,b^-), SHC\left(Y7_p,pi\right)$
r38: $EGFR\left(Y48^2_p\right), GRB2\left(a,b^1\right), SHC\left(Y7_p,pi^2\right), SOS\left(d^1\right) \longrightarrow EGFR\left(Y48^3_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^3\right), SOS\left(d^1\right)$
r39: $EGFR\left(Y48^3_p\right), GRB2\left(a^2,b^1\right), SHC\left(Y7^2_p,pi^3\right), SOS\left(d^1\right) \longrightarrow EGFR\left(Y48^2_p\right), GRB2\left(a,b^1\right), SHC\left(Y7_p,pi^2\right), SOS\left(d^1\right)$

We start with the following initial state:

$$2000 * (EGFR(l,r,Y48_u,Y68_u))$$
$$2000 * (EGF(r))$$
$$2000 * (GRB2(a,b))$$
$$1000 * (SOS(d))$$
$$1000 * (SHC(pi,Y7_u))$$

2 First intuitions about the model

(i) Compute the contact map for this model.
$\Longrightarrow$ *(with the KappaFactory)*

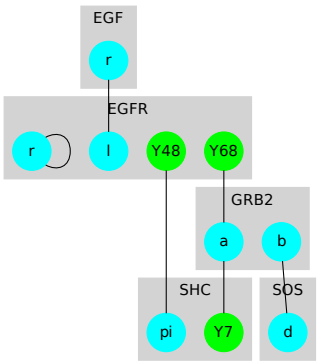


Fig. 1. Contact map

1. *Import (Menu 'File' → 'Import' → 'KappaFile') the file* `egfr.ka` *in the Factory;*
2. *Select the tab 'Contact Map';*
3. *Click on the button 'Generate Contact Map'.*

$\Longrightarrow$ *(with complx and graphviz)*

1. *Put* `egfr.ka` *in the same repository than* `complx`*;*
2. *Prompt* `./complx --reset-all egfr.ka --do-high-res-contact-map --output-high-res-contact-map-dot contact_map.dot;`
3. *Prompt* `dot -Tpdf contact_map.dot -o contact_-map.pdf;`
4. *The contact map in Fig. 1 is now in the file* `contact_map.pdf`*.*

□

In this model, some receptors *EGFR* recruit some proteins *SOS*. This can be done in two different ways:

- a receptor *EGFR* can be bound to a protein *GRB2* that is bound to a protein *SOS (short arm)*;
- a receptor *EGFR* can be bound to a protein *SHC* that is bound to a protein *GRB2*, that is bound to a protein *SOS (long arm)*.

(ii) Compute the *stories* that describe how a receptor *EGFR* can recruit a protein *SOS*.

$\Longrightarrow$ *(with the KappaFactory)*

1. *Select the tab 'Stories';*
2. *Check the two rules with the name 'short' and the name 'long';*
3. *Select the option 'Weak' compression;*

4. *Increase the number of events to* 1000000 *and the number of iterations to* 50*;*
5. *Click on the button 'Run stories'.*

$\Longrightarrow$ *(with simplx and graphviz)*

1. *Put* `egfr.ka` *in the same repository than* `simplx`*;*
2. *Prompt* `./simplx --cflow egfr.ka --iteration 50 --event 1000000 --dot-output`*;*
3. *Prompt* `ls h*.dot`*;*
4. *For any obtained file, say* `h0.dot`*, prompt* `dot -Tpdf h0.dot -o h0.pdf`*, so as to convert the story in pdf.*

We give in Fig. 2 the two possible stories (since the simulation is stochastic, it may happen that only one story is found during a set of simulations).

□

(iii) Compute the number of reachable species.

There are 356 *reachable species.*

$\Longrightarrow$ *(with the KappaFactory)*

1. *Select the tab 'Reachables';*
2. *Check the box 'Enumerate Complexes';*
3. *Click on the button 'Generate Reachables'.*

$\Longrightarrow$ *(with complx)*

1. *Put* `egfr.ka` *in the same repository than* `complx`*;*
2. *Prompt* `./complx egfr.ka --reset-all --enumerate-complexes --output-reachable-complexes species.txt`*;*
3. *Prompt* `tail species.txt`*.*

□

(iv) Is it possible for a receptor *EGFR* to be bound to another receptor *EGFR* while not being bound to a ligand *EGF* ?

No, because on the first hand a receptor can bind another receptor only if these two receptors are activated (r03) and on the second hand the bond between a ligand and a receptor can be released only if the dimerisation site is free (r01).

Let us use the engine to prove this fact.

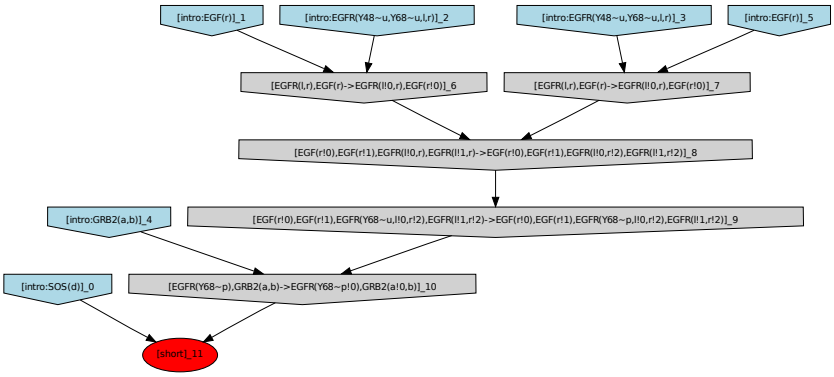
Let us add the following silent rule:

$$EGFR(l,r^-) \longrightarrow EGFR(l,r^-)$$

to the kappa file `egfr.ka`*.*

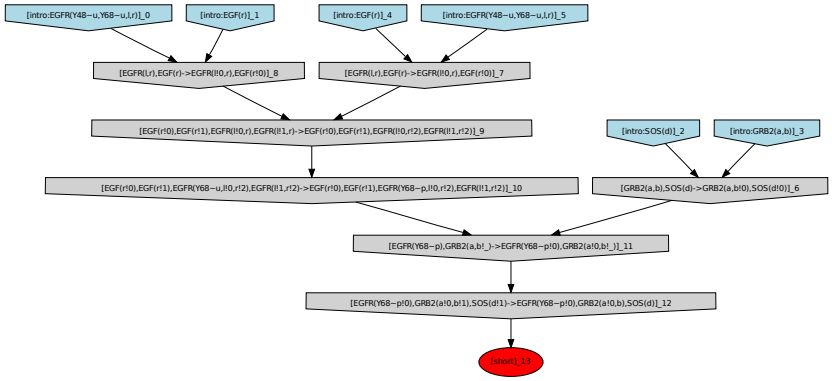
$\Longrightarrow$ *(with the KappaFactory)*

1. *Import (Menu 'File' $\rightarrow$ 'Import' $\rightarrow$ 'KappaFile') the file* `egfr.ka` *in the Factory;*
2. *Select the tab 'Compression';*



Observed 48 times after an average of 0.0441t.u (from egfr.ka)

(a) short arm



Observed 2 times after an average of 0.0329t.u (from egfr.ka)

(b) long arm

Fig. 2. Stories

3. *Select the option 'quantitative' compression;*
4. *Click on the button 'Perform Compression'.*

The added rule is displayed in red which means that its left hand side never occurs at run time (which was what we wanted to prove).

$\Longrightarrow$ *(with complx)*

1. *Prompt* `./complx egfr.ka > Log;`
2. *Prompt* `grep applied Log;`

The analyzer has proved that the silent rule can never be applied.

3 Internal coarse graining

(i) Use the software to compute the reduced differential systems that is associated with our rule set. How many fragments are there?
$\Longrightarrow$ (with complx)

1. Prompt `./complx egfr.ka --reset-all --do-ODE --output-scheme egfr --final-time 6` ;
2. Prompt `ls *kappa_ODE*`;
3. Prompt `less egfr_kappa_ODE_system_size.m`.

There are 83 fragments.

□

(ii) Argue that the rule `r04` can be replaced with a simpler rule without modifying the behavior of the model.

According to the contact map (Fig. 1), the sire r of a receptor can only be bound to the site r of another receptor. Moreover, according to question (2.iv), whenever the site r of a receptor is bound, the site l of the same receptor is also bound (to a ligand according to the contact map (Fig. 1). As a consequence, whenever the site r of a receptor is bound, we have two receptors bounds to two ligands and a bond between the two receptors. Thus the rule can be replaced with the following one:

$$EGFR(r^-) \longrightarrow EGFR(r).$$

□

(iii) Use the software to compress the rule set.
$\Longrightarrow$ (with the KappaFactory)

1. Select the tab 'Compression';
2. Select the option 'quantitative' compression;
3. Click on the button 'Perform Compression'.

This output cannot be bootstrapped into the factory.
$\Longrightarrow$ (with complx)

1. Prompt `./complx --reset-all --compute-quantitative-compression egfr.ka --output-quantitative-compression egfr_compressed.ka`

A new file `egfr_compressed.ka` is created. This file contains the foolowing compressed rules:

rc01: $EGF(r)$, $EGFR(l) \longrightarrow EGF(r^1)$, $EGFR(l^1)$
rc02: $EGFR(l^-,r) \longrightarrow EGFR(l,r)$
rc03: $EGFR(l^-,r)$, $EGFR(l^-,r) \longrightarrow EGFR(l^-,r^1)$, $EGFR(l^-,r^1)$
rc04: $EGFR(r^-) \longrightarrow EGFR(r)$ @0.5
rc05: $EGFR(Y68^?_u,r^-) \longrightarrow EGFR(Y68^?_p,r^-)$
rc06: $EGFR(Y68_p) \longrightarrow EGFR(Y68_u)$
rc07: $EGFR(Y48^?_u,r^-) \longrightarrow EGFR(Y48^?_p,r^-)$
rc08: $EGFR(Y48_p) \longrightarrow EGFR(Y48_u)$
rc09: $EGFR(Y48^1,r^-)$, $SHC(Y7^?_u,pi^1) \longrightarrow EGFR(Y48^1,r^-)$, $SHC(Y7^?_p,pi^1)$
rc10: $SHC(Y7_p,pi^-) \longrightarrow SHC(Y7_u,pi^-)$
rc11: $SHC(Y7_p,pi) \longrightarrow SHC(Y7_u,pi)$
rc12: $EGFR(Y68_p)$, $GRB2(a,b) \longrightarrow EGFR(Y68^1_p)$, $GRB2(a^1,b)$
rc13: $EGFR(Y68^1)$, $GRB2(a^1,b) \longrightarrow EGFR(Y68)$, $GRB2(a,b)$
rc14: $EGFR(Y68_p)$, $GRB2(a,b^-) \longrightarrow EGFR(Y68^1_p)$, $GRB2(a^1,b^-)$
rc15: $EGFR(Y68^1)$, $GRB2(a^1,b^-) \longrightarrow EGFR(Y68)$, $GRB2(a,b^-)$
rc16: $EGFR(Y68^1)$, $GRB2(a^1,b)$, $SOS(d) \longrightarrow EGFR(Y68^2)$, $GRB2(a^2,b^1)$, $SOS(d^1)$
rc17: $EGFR(Y68^1)$, $GRB2(a^1,b^-) \longrightarrow EGFR(Y68^1)$, $GRB2(a^1,b)$
rc18: $GRB2(a,b)$, $SOS(d) \longrightarrow GRB2(a,b^1)$, $SOS(d^1)$
rc19: $GRB2(a,b^-) \longrightarrow GRB2(a,b)$
rc20: $GRB2(a^1,b)$, $SHC(Y7^1,pi)$, $SOS(d) \longrightarrow GRB2(a^2,b^1)$, $SHC(Y7^2,pi)$, $SOS(d^1)$
rc21: $GRB2(a^1,b^-)$, $SHC(Y7^1,pi) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1,pi)$
rc22: $GRB2(a^1,b)$, $SHC(Y7^1,pi^-)$, $SOS(d) \longrightarrow GRB2(a^2,b^1)$, $SHC(Y7^2,pi^-)$, $SOS(d^1)$
rc23: $GRB2(a^1,b^-)$, $SHC(Y7^1,pi^-) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1,pi^-)$
rc24: $EGFR(Y48_p)$, $SHC(Y7^?_u,pi) \longrightarrow EGFR(Y48^1_p)$, $SHC(Y7^?_u,pi^1)$
rc25: $SHC(Y7^?_u,pi^-) \longrightarrow SHC(Y7^?_u,pi)$
rc26: $EGFR(Y48_p)$, $SHC(Y7_p,pi) \longrightarrow EGFR(Y48^1_p)$, $SHC(Y7_p,pi^1)$
rc27: $SHC(Y7_p,pi^-) \longrightarrow SHC(Y7_p,pi)$
rc28: $EGFR(Y48_p)$, $GRB2(a^1,b)$, $SHC(Y7^1,pi) \longrightarrow EGFR(Y48^2_p)$, $GRB2(a^1,b)$, $SHC(Y7^1,pi^2)$
rc29: $GRB2(a^1,b)$, $SHC(Y7^1,pi^-) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1,pi)$
rc30: $EGFR(Y48_p)$, $GRB2(a^1,b^-)$, $SHC(Y7^1,pi) \longrightarrow EGFR(Y48^2_p)$, $GRB2(a^1,b^-)$, $SHC(Y7^1,pi^2)$
rc31: $GRB2(a^1,b^-)$, $SHC(Y7^1,pi^-) \longrightarrow GRB2(a^1,b^-)$, $SHC(Y7^1,pi)$
rc32: $GRB2(a,b)$, $SHC(Y7_p,pi^-) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1_p,pi^-)$
rc33: $GRB2(a^1,b)$, $SHC(Y7^1,pi^-) \longrightarrow GRB2(a,b)$, $SHC(Y7,pi^-)$

rc34: $GRB2(a,b)$, $SHC\left(Y7_p,pi\right) \longrightarrow GRB2\left(a^1,b\right)$, $SHC\left(Y7_p^1,pi\right)$
rc35: $GRB2\left(a^1,b\right)$, $SHC\left(Y7^1,pi\right) \longrightarrow GRB2(a,b)$, $SHC(Y7,pi)$
rc36: $GRB2(a,b^-)$, $SHC\left(Y7_p,pi\right) \longrightarrow GRB2\left(a^1,b^-\right)$, $SHC\left(Y7_p^1,pi\right)$
rc37: $GRB2\left(a^1,b^-\right)$, $SHC\left(Y7^1,pi\right) \longrightarrow GRB2(a,b^-)$, $SHC(Y7,pi)$
rc38: $GRB2(a,b^-)$, $SHC\left(Y7_p,pi^-\right) \longrightarrow GRB2\left(a^1,b^-\right)$, $SHC\left(Y7_p^1,pi^-\right)$
rc39: $GRB2\left(a^1,b^-\right)$, $SHC\left(Y7^1,pi^-\right) \longrightarrow GRB2(a,b^-)$, $SHC(Y7,pi^-)$

□.

(iv) Explain the kinetic factor of the rule `r04` in the compressed rule set.

Let us denote by k the kintetic rate of the rule r04 and by k' the kinetic rate of the rule rc04. Let x be a mixture. We know that the number of embeddings of the left hand side of r04 into the mixture x and the number of embeddings of the left hand side of rc04 into the mixture x are the same (this is a property of quantitative compression). Let us denote this number by $n(x)$ (we assume that $n(x) > 0$). Then, we want these two rules to have the same activity, which gives the following equations:

$$\frac{k \times n(x)}{|Aut(lhs(\text{r04}))|} = activivity = \frac{k' \times n(x)}{|Aut(lhs(\text{rc04}))|}$$

Then:

$$\frac{k \times n(x)}{2} = \frac{k' \times n(x)}{1}$$

And:

$$k' = \frac{k}{2}.$$

□

(v) Use the software to compute the reduced differential systems that is associated with compressed rule set. How many fragments are there?

$\Longrightarrow$ (with complx)

1. Prompt `./complx egfr_compressed.ka --reset-all --do-ODE --output-scheme egfr_compressed --final-time 6`;
2. Prompt `ls *compressed_kappa_ODE*`;
3. Prompt `less egfr_compressed_kappa_ODE_system_size.m`.

There are 38 fragments.

□

The reduction used the annotated contact map that is given in Fig. 3.

(vi) Motivate each solid/strong edge and each covering class.

– *solid edges:*

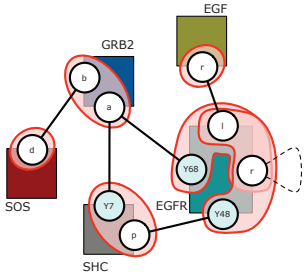


Fig. 3. annotated contact map.

- *the edge between EGF and EGFR is solid because of the rule rc02 (it can be released by a rule testing something else);*
- *the edge between EGFR and GRB2 is solid because of the rule rc13 (or equivalently rc15, rc16, or rc17);*
- *the edge between EGFR and SHC is solid because of the rule rc09 (or equivalently rc25, rc29, or rc31);*
- *the edge between GRB2 and SOS is solid because of the rule rc17 (or equivalently rc19, rc21, or rc23);*
- *the edge between SHC and GRB2 is solid because of the rule rc20 (or equivalently rc21, rc22, rc23, rc28, rc29, rc30, rc31, rc33, rc35, rc37, rc39);*

– *covering classes:*

- *EGFR*
  - *any class containing the site l should contain the site r because of the rule rc02;*
  - *any class containing the site r should contain the site l, because of the rule rc03;*
  - *any class containing the site Y48 should contain the site r, because of the rule rc07 (or equivalently rc09);*
  - *any class containing the site Y68 should contain the site r, because of the rule rc05;*
- *GRB2*
  - *any class containing the site a should contain the site b, because of the rule rc12 (or equivalently rc13, rc14, rc15, rc16, rc28, rc29, rc30, rc31, rc32, rc33, rc34, rc35, rc36, rc37, rc38, or rc39);*
  - *any class containing the site b should contain the site a, because of the rule rc16 (or equivalently rc17, rc18, rc19, rc20, rc21, rc22, rc23);*
- *SHC*
  - *any class containing the site Y7 should contain the site pi, because of the rule rc09 (or equivalently rc10, rc11, rc20, rc21, rc22, rc23, rc32, rc33, rc34, rc35, rc36, rc37, rc38, or rc39);*

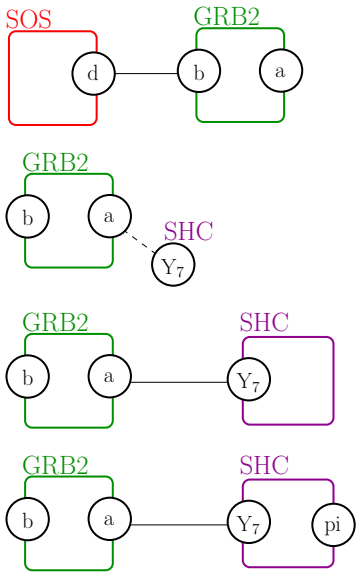


Fig. 4. fragment candidates

- ∗ *any class containing the site pi should contain the site Y7, because of the rule rc24 (or equivalently rc25, rc26, rc27, rc28, rc29, rc30, or rc31).*

That is all the constraints that we have.

□

(vii) Which subspecies in Fig. 4 are fragments with respect to the annotated contact map given Fig. 3 ?

1. *The first one because (i) the bond is solid in the annotated contact map as well and (ii) the set* $\{a, b\}$ *forms a covering class;*
2. *the second one is not a fragment, because the edge between the site a of GRB2 and the site Y7 of SHC is solid in the annotated contact map;*
3. *the third one is not a fragment because the set* $\{Y7\}$ *is not a covering class;*
4. *the fourth one is a fragment because (i) the bond is solid in the annotated contact map as well, (ii) the set* $\{a, b\}$ *forms a covering class, and (iii) the set* $\{Y7, pi\}$ *forms a covering class.*

□

(viii) Explain why, with the initial rule set, the edge between the site r of the agent *EGFR* and itself, should be solid/strong.

The edge should have been solid due to the rule r04 (or equivalently r05, or r07). All these rules have been simplified by the rule compression.

□

(ix) Plot the concentration of the proteins *SOS* that are attached to a receptor according to the simulation time.

$\Longrightarrow$ *(with octave (with the package odepkg) and gnuplot)*

1. *Prompt* `octave egfr_compressed_kappa_ODE_system.m;`
2. *Prompt* `gnuplot egfr_compressed_kappa_ODE.gplot.`

The file `egfr_compressed_kappa_ODE.data`*, in Fig. 5 is created.*

□

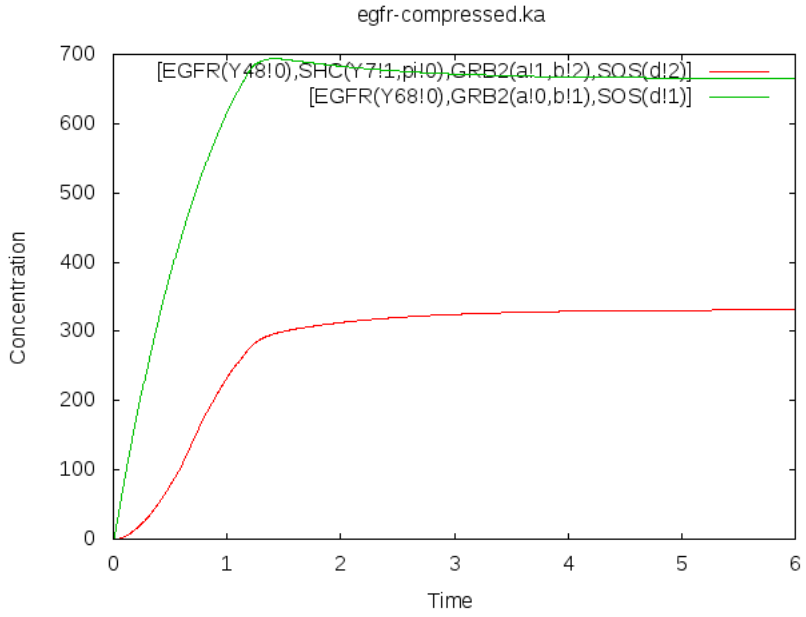


Fig. 5. Concentrations of SOS attached to the membrane with respect to simulation time.

□