Fragmenting the early EGFR pathway

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All along this pratical work, by “fragments”, we mean homogeneous fragments (ie. the fragments which can be generated from a non oriented contact map). Heterogeneous fragments are not implemented yet.

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: $GRB2(a^1,b)$, $SHC(Y7^1_p,pi^-)$, $SOS(d) \longrightarrow GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^-)$, $SOS(d^1)$

r23: $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^-)$, $SOS(d^1) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1_p,pi^-)$, $SOS(d)$

r24: $EGFR(Y48_p)$, $SHC(Y7_u,pi) \longrightarrow EGFR(Y48^1_p)$, $SHC(Y7_u,pi^1)$

r25: $EGFR(Y48^1_p)$, $SHC(Y7_u,pi^1) \longrightarrow EGFR(Y48_p)$, $SHC(Y7_u,pi)$

r26: $EGFR(Y48_p)$, $SHC(Y7_p,pi) \longrightarrow EGFR(Y48^1_p)$, $SHC(Y7_p,pi^1)$

r27: $EGFR(Y48^1_p)$, $SHC(Y7_p,pi^1) \longrightarrow EGFR(Y48_p)$, $SHC(Y7_p,pi)$

r28: $EGFR(Y48_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi) \longrightarrow EGFR(Y48^2_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi^2)$

r29: $EGFR(Y48^2_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi^2) \longrightarrow EGFR(Y48_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi)$

r30: $EGFR(Y48_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi)$, $SOS(d^1) \longrightarrow EGFR(Y48^3_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^3)$, $SOS(d^1)$

r31: $EGFR(Y48^3_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^3)$, $SOS(d^1) \longrightarrow EGFR(Y48_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi)$, $SOS(d^1)$

r32: $EGFR(Y48^1_p)$, $GRB2(a,b)$, $SHC(Y7_p,pi^1) \longrightarrow EGFR(Y48^2_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi^2)$

r33: $EGFR(Y48^2_p)$, $GRB2(a^1,b)$, $SHC(Y7^1_p,pi^2) \longrightarrow EGFR(Y48^1_p)$, $GRB2(a,b)$, $SHC(Y7_p,pi^1)$

r34: $GRB2(a,b)$, $SHC(Y7_p,pi) \longrightarrow GRB2(a^1,b)$, $SHC(Y7^1_p,pi)$

r35: $GRB2(a^1,b)$, $SHC(Y7^1_p,pi) \longrightarrow GRB2(a,b)$, $SHC(Y7_p,pi)$

r36: $GRB2(a,b^-)$, $SHC(Y7_p,pi) \longrightarrow GRB2(a^1,b^-)$, $SHC(Y7^1_p,pi)$

r37: $GRB2(a^1,b^-)$, $SHC(Y7^1_p,pi) \longrightarrow GRB2(a,b^-)$, $SHC(Y7_p,pi)$

r38: $EGFR(Y48^2_p)$, $GRB2(a,b^1)$, $SHC(Y7_p,pi^2)$, $SOS(d^1) \longrightarrow EGFR(Y48^3_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^3)$, $SOS(d^1)$

r39: $EGFR(Y48^3_p)$, $GRB2(a^2,b^1)$, $SHC(Y7^2_p,pi^3)$, $SOS(d^1) \longrightarrow EGFR(Y48^2_p)$, $GRB2(a,b^1)$, $SHC(Y7_p,pi^2)$, $SOS(d^1)$

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.

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*.
(iii) Compute the number of reachable species.
(iv) Is it possible for a receptor *EGFR* to be bound to another receptor *EGFR* while not being bound to a ligand *EGF* ?

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?
hint: `complx egfr.ka --reset-all --do-ODE --output-scheme egfr --final-time 6`
(ODE files have the prefix `egfr_plx_ODE`).
(ii) Argue that the rule `r04` can be replaced with a simpler rule without modifying the behaviour of the model.
(iii) Use the software to compress the rule set.
hint: `complx --reset-all --compute-quantitative-compression egfr.ka --output-quantitative-compression egfr_compressed.ka`
(iv) Explain the kinetic factor of the rule `r04` in the compressed rule set.
(v) Use the software to compute the reduced differential systems that is associated with compressed rule set. How many fragments are there?

The reduction used the annotated contact map that is given in Fig. 1.

(vi) Motivate each solid/strong edge and each covering class.
(vii) Which subspecies in Fig. 2 are fragments with respect to the annotated contact map given Fig. 1 ?
(viii) Explain why, with the initial rule set, the edge between the site r of the agent *EGFR* and itself, should be solid/strong.
(ix) Plot the concentration of the proteins *SOS* that are attached to a receptor according to the simulation time.
hint: Use either Octave or Matlab to run the file `egfr_plx_ODE_system.m`. It will generate the files `egfr_plx.data`, `egfr_plx_head.data` and `egfr_plx_ODE.gplot`.

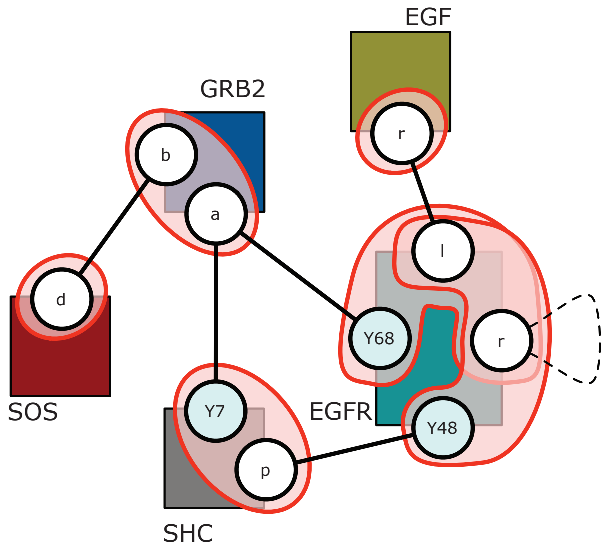

Fig. 1. annotated contact map.

4 More complex example

Now, we consider that the bond between a ligand *EGF* and a receptor *EGFR* can be broken even if the receptor is bound to another receptor.

(i) Encode this assumption as a kappa rule.
(ii) How is modified the annotated contact map and the set of fragments? Do you think the reduction that is obtained thanks to the application is optimal?

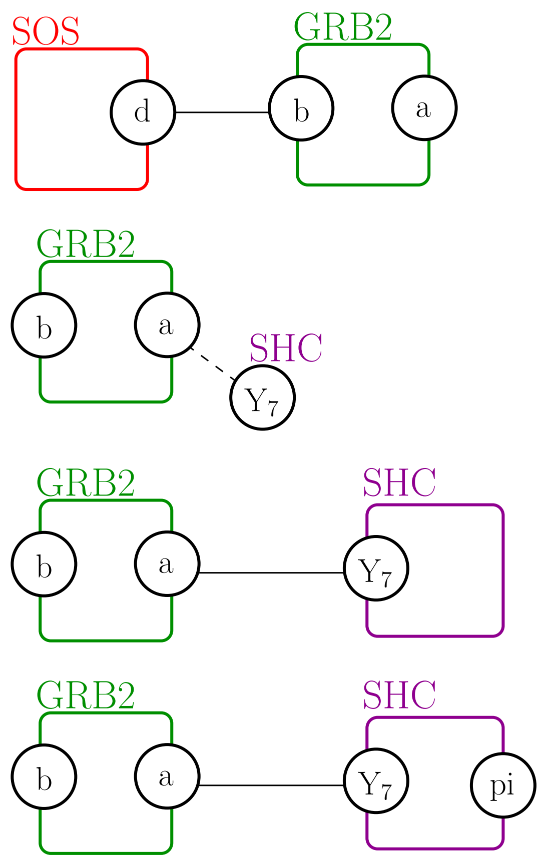

Fig. 2. fragment candidates