2.0 Visinets Simulation Engine

2.1. Analytical description of CMAP.

A causal map is a graph in which the components (concepts) are the nodes (species), and causal influences are the edges. The behavior of each species Cj(t) is described by the following basic CMAP equations:

$$C_j(t) = C_j(t-1) + \Lambda_j(C_j(t-1), f_j) * f_j(W_{ij}, C_i(t-1)) \tag{1a}$$

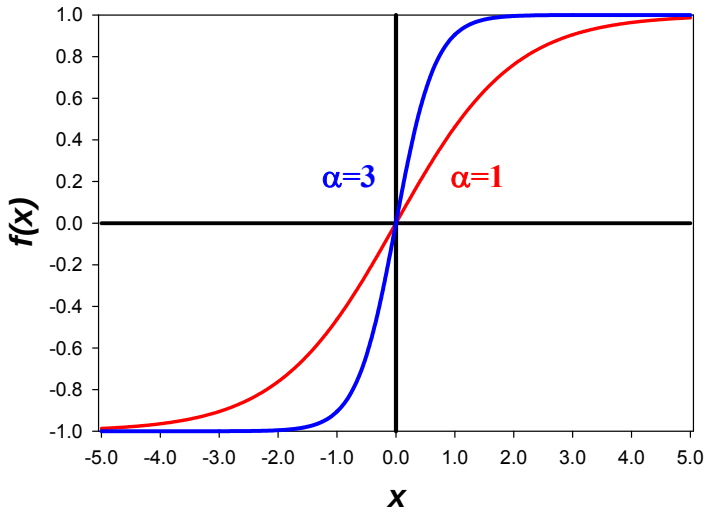
$$f_j \equiv f(x_j) = \frac{1-e^{-\alpha_j x_j}}{1+e^{-\alpha_j x_j}}, \quad x_j = \sum_{i=1}^{N} C_i W_{ij} + \sum_{i=1}^{N}\sum_{k=1}^{N} C_i C_k W_{ikj} + \ldots + \sum_{i=1}^{N}\ldots\sum_{l=1}^{N} C_i \ldots C_l W_{i\ldots lj};$$

$$\Lambda_j(C_j(t), f_j) = \begin{cases} C_j^{\max} - C_j(t), & \text{if } f_j > 0, \\ C_j(t), & \text{if } f_j \le 0, \end{cases} \tag{1b}$$

The species ($C_j(t)$) can assume any value between 0 and 1 and are variable. They represent species concentration and/or combination of concentration and activity. The weights (W_{ij}, strengths of influences reflecting the chemical rate constants, e.g. k_1, k_2, and k_{cat}) are constant during simulations. The absolute values of the weights are also normalized and limited to the same interval. Each influence may be assigned positive or negative value (activation or inhibition) and carry positive or negative numerical value graphically depicted in green or red respectively **(Fig. 19 & 20)**. Multiple inputs are added and/or subtracted, depending on their values. The right side of **Eq. (1a)** contains two factors. Λ_j restricts the species to the 0-1 scaled interval. The causal function f_j includes all influences from the system (including self-influence, red line attached to one species only) **(Fig. 19 & 20)** on a given species $C_j(t)$.

$$f(x_j) = \frac{1 - e^{-\alpha x_j}}{1 + e^{-\alpha x_j}}$$

Figure 18



Parameter α in **Eq. (1b)** determines the sensitivity of a response of a species to a given input **(Figure 18).** In other words, α may be used to increase the species responsiveness to change in inputs. i.e. the response time scale.

2.2. Graphical description of CMAP

Elemental influences. The basic idea of the causal map is to graphically represent all the components of the system of interest along with all interactions between them with an underlying aim to replace mathematical descriptions using formulas by graphical means. While it requires simplification and generalization of the mathematical framework, it provides the power of graphical user-computer interaction and is a useful tool for those without rigorous training of mathematics of physics and chemistry. **Figure 19** illustrates the elemental connections (influences) of the causal map. In the context of biochemical reactions that take place in signaling pathways, these principles may be further extended to protein-protein interactions (for example receptor-ligand interaction) and/or enzymatic reaction (protein phosphorylation).

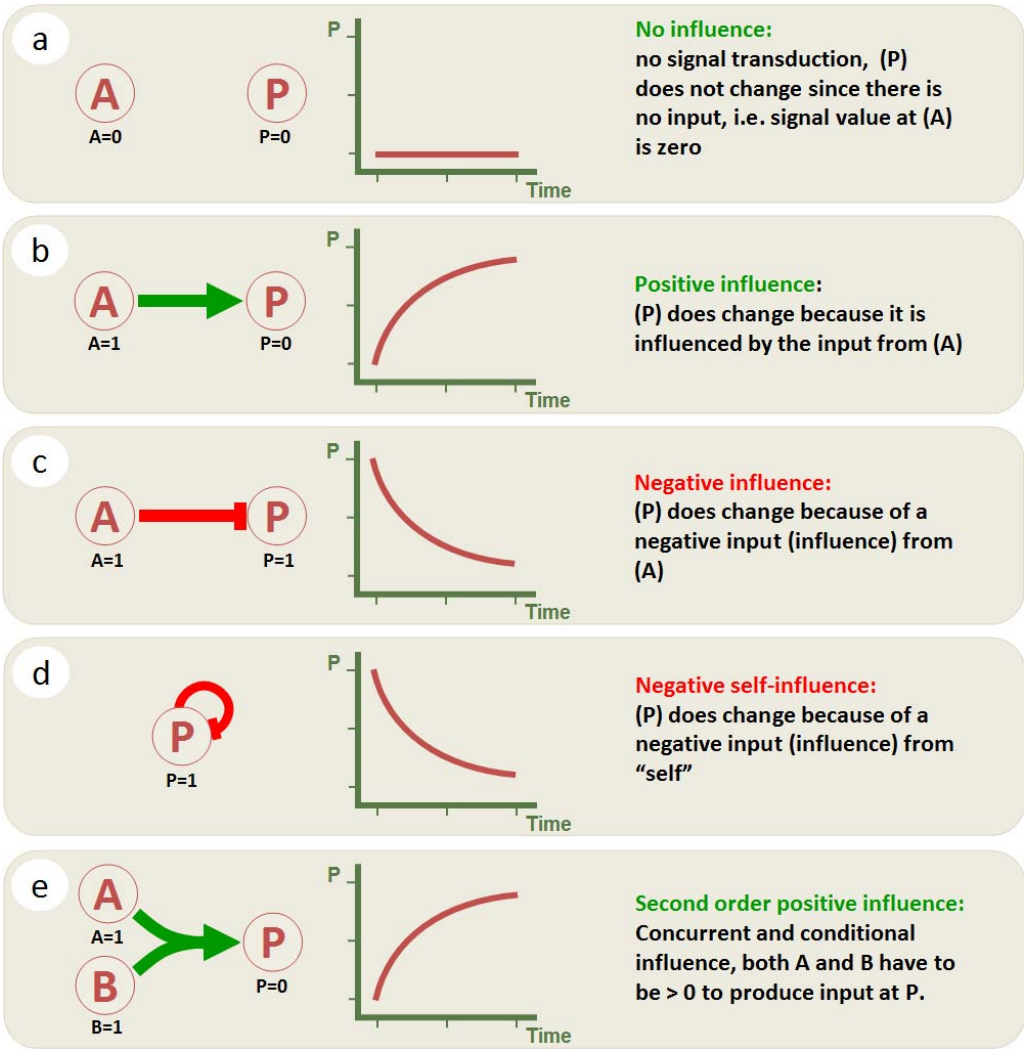


Figure 19

Binding and enzymatic reaction modules and their correspondence to ODE formalism. Each binding or enzymatic reaction may be drawn manually or incorporated as a partially pre-assembled functional module using the "construct" function as described in **Quick Start: 1.4. How to create binding reaction module** and/or **1.5. How to create enzymatic reaction module.**

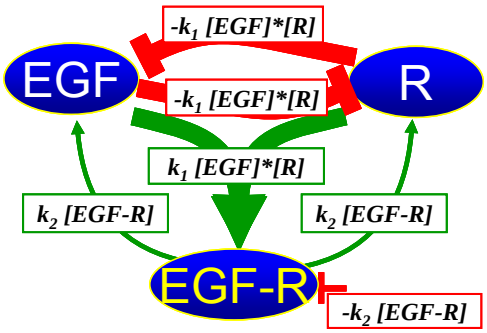
To better illustrate how CMAP formalism works, the more detailed comparison of ODE expressions with CMAP graphical influences are shown in **Fig. 20 & 21**, where ODEs chemical kinetics and CMAP graphical representation for a binding and enzymatic reactions are shown side-by-side. In **Fig. 20**, depicting the example of EGF binding to its receptor as a binding reaction module, the chemical kinetics formalism **(A)** and a corresponding CMAP representation **(B)**, and full one-to-one translation of all ODE terms into influences, are listed **(C).** In **Fig 21** the same is shown for an enzymatic reaction. In cases where enzyme remains in complex with the product, which is a common occurrence in signaling pathways, the influence representing kcat from the SE to Enz. needs to be manually removed. Note the presence of negative self influence on the enzyme/protein complex.

Figure 20

A. Kinetic formalism

$$\frac{d[EGF]}{dt} = k_2[EGF-R] - k_1[EGF][R]$$
$$\frac{d[R]}{dt} = k_2[EGF-R] - k_1[EGF][R]$$
$$\frac{d[EGF-R]}{dt} = k_1[EGF][R] - k_2[EGF-R]$$

B. Graphical representation



C. Principles of ODE to CMAP translation

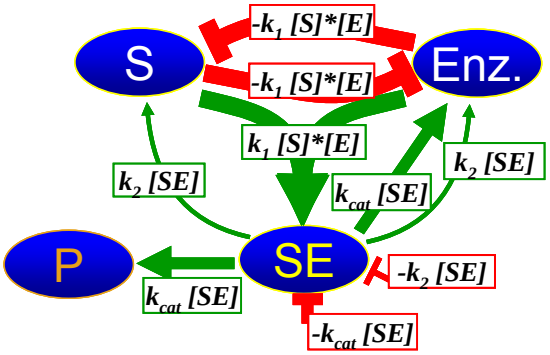
#	Species	ODE expressions	CMAP Influences
1	R	-k1*[R]*[EGF]+k2*[EGF-R]	- R*EGF +EGF-R
2	EGF	-k1*[R]*[EGF]+k2*[EGF-R]	- R*EGF +EGF-R
3	EGF-R	k1*[R]*[EGF]-k2*[EGF-R]	+R*EGF -EGF-R

Figure 21

A. Kinetic formalism

$$\frac{d[E]}{dt} = k_2[SE] + k_{cat}[SE] - k_1[E][S]$$
$$\frac{d[S]}{dt} = k_2[SE] - k_1[E][S]$$
$$\frac{d[SE]}{dt} = k_1[E][S] - k_2[SE] - k_{cat}[SE]$$
$$\frac{d[P]}{dt} = k_{cat}[SE]$$

B. Graphical representation



C. Principles of ODE to CMAP translation

#	Species	ODE expressions	CMAP Influences
1	S	- k1*[S]*[E]+k2*[SE]	- S*E +SE
2	E	- k1*[S]*[E]+k2*[SE]	- S*E +SE
		kcat*[SE]	+SE
3	SE	k1*[S]*[E]-k2*[SE]	+S*E -SE
		-kcat*[SE]	-SE
4	P	kcat*[SE]	+SE

These two examples additionally explain the rules governing proper grouping of weights. In the context of binding reaction, the weights for all [EGF]*[R] influences and [EGF-R] (both positive and negative) influences, need to be grouped. In enzymatic reaction k_{cat} [SE] (all 3 occurrences) need to be also grouped. In effect, changing one forward, or one reverse reaction rate constant (weight), will change the whole grouped set.

3. Troubleshooting

A. Drawing problems and solutions

3.1. I have accidentally created two or more handle points on the influence (arrow). To remove unwanted handle points and create a smooth arch for the influence drag one of the handle on top of the other and they automatically become one. Repeat with the remaing unwanted points, if necessary.

3.2. Undo button may sometimes restore the connections incorrectly. When accidentally deleting one species that is connected with multiple other species, the undo function may not re-connect all the connections and the user needs to carefully check these connections manually

3.3. Adjusting the Spiecies position by small increments. When you need fine positions adjustments of objects, or when you can't get snap-to-grid properly, hold the Shift key down and move the object using mouse.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