Notes on the derivation and brief documentation of SysBio library

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Abstract

This document describes the derivation of the equations describing the fundamental object classes of SysBio library that is used to represent enzyme catalysed reaction following Michaelis-Menten kinetics according to [Belič et al., 2013, Naik, 2013, Naik et al., 2014]. The derivation is followed with a brief documentation of basic SysBio library object classes, i.e:

- enzyme catalysed reaction (ESReaction),
- substrate sources (ESource and Source),
- metabolite (Metabolite),
- enzyme (Enzyme),
- non-enzymatic protein (Protein),
- mRNA (mRNA),
- transcription regulation (GeneExpressionControl_positive, GeneExpressionControl_negative and GeneExpressionControl_lin),
- translation (EFormation_lin),
- post-translational regulation (Activation and Inhibition).

All descriptions presume the normalised steady state concentration of observed compounds.

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Contents

1 Derivation of enzyme catalysed reaction in normalised steady state

Enzyme catalysed reaction in normalised steady state are derived according to the reaction system described in Figure 1, where the parameters have the following interpretation:

- f: proportion of the metabolic flux into alternative pathways,
- $1 - f$: proportion of the metabolic flux into pathway of interest,
- Φ_I: substrate influx,
- Φ_{EI}: enzyme influx,
- Φ_O: product outflux,
- S: substrate concentration,
- E: enzyme concentration,
- C: complex concentration,
- P: product concentration,
- k_C: complex formation constant,
- k_{CR}: complex dissociation constant,
- k_P: product formation constant,
- k_{PR}: product dissociation constant.

1.1 Basic ODE description

$$S : \frac{dS}{dt} = \Phi_I(1 - f) - k_C \cdot E \cdot S + k_{CR} \cdot C \tag{1}$$

$$C : \frac{dC}{dt} = k_C \cdot E \cdot S + k_{PR} \cdot E \cdot P - k_P \cdot C - k_{CR} \cdot C \tag{2}$$

$$P : \frac{dP}{dt} = k_P \cdot C - \Phi_O - k_{PR} \cdot E \cdot P \tag{3}$$

$$E : \frac{dE}{dt} = \Phi_{EI} + k_P \cdot C + k_{CR} \cdot C - k_C \cdot E \cdot S - k_{PR} \cdot E \cdot P - \Phi_{EO} \tag{4}$$

1.2 Steady state presumption

Presumptions

- All changes equal to zero: $\frac{dS}{dt} = \frac{dC}{dt} = \frac{dP}{dt} = \frac{dE}{dt} = 0$.
- Influxes equal to efluxes: $\Phi_I(1 - f) = \Phi_O$, $\Phi_{EI} = \Phi_{EO}$

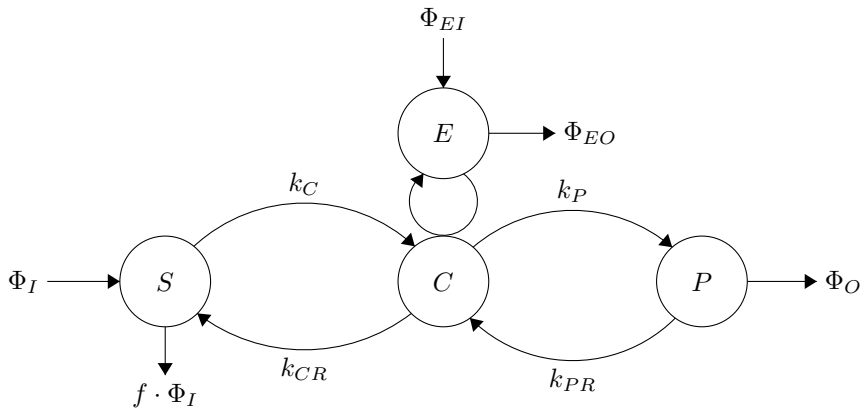

Figure 1: Enzyme catalysed reaction according to Michaelis-Menten kinetic formalism.

Equations

$$S : 0 = \Phi_I(1-f) - k_C \cdot E \cdot S + k_{CR} \cdot C \tag{5}$$
$$C : 0 = k_C \cdot E \cdot S + k_{PR} \cdot E \cdot P - k_P \cdot C - k_{CR} \cdot C \tag{6}$$
$$P : 0 = k_P \cdot C - \Phi_O - k_{PR} \cdot E \cdot P \tag{7}$$
$$E : 0 = k_P \cdot C + k_{CR} \cdot C - k_C \cdot E \cdot S - k_{PR} \cdot E \cdot P \tag{8}$$

1.3 Normalisation of concentrations

Presumptions

- We can vonvert concentrations (S, E, C and P) to normalised values (S_N, E_N, C_N and P_N) at steady state (S_{SS}, E_{SS}, C_{SS} and P_{SS}).
- $S_N = \frac{S}{S_{SS}}$
- $E_N = \frac{E}{E_{SS}}$
- $P_N = \frac{P}{P_{SS}}$

Complex concentration (C_N) must be expressed relative to the free enzyme concentrations at steady state:

- Ratio between bound and free enzyme equals $w = \frac{C_{SS}}{E_{SS}}$.
- $C_N = \frac{C}{E_{SS}} = \frac{w \cdot C}{C_{SS}}$

Therefore:

- $S = S_N \cdot S_{SS}$

- $E = E_N \cdot E_{SS}$
- $C = \frac{C_N \cdot C_{SS}}{w}$
- $P = P_N \cdot P_{SS}$

Equations

Substrate consumption (inserting normalisation presumptions into Equation 5):

$$S: \ 0 = \Phi_I(1-f) - k_C \cdot E_N \cdot E_{SS} \cdot S_N \cdot S_{SS} + k_{CR} \cdot \frac{C_N \cdot C_{SS}}{w} \tag{9}$$

Complex formation (inserting normalisation presumptions into Equation 6):

$$C: \ 0 = k_C \cdot E_N \cdot E_{SS} \cdot S_N \cdot S_{SS} + k_{PR} \cdot E_N \cdot E_{SS} \cdot P_N \cdot P_{SS} - k_P \cdot \frac{C_N \cdot C_{SS}}{w} - k_{CR} \cdot \frac{C_N \cdot C_{SS}}{w} \tag{10}$$

Product formation (inserting normalisation presumptions into Equation 7):

$$P: \ 0 = k_P \cdot \frac{C_N \cdot C_{SS}}{w} - \Phi_O - k_{PR} \cdot E_N \cdot E_{SS} \cdot P_N \cdot P_{SS} \tag{11}$$

Enzyme dynamics (inserting normalisation presumptions into Equation 8):

$$E: \ 0 = k_P \cdot \frac{C_N \cdot C_{SS}}{w} + k_{CR} \cdot \frac{C_N \cdot C_{SS}}{w} - k_C \cdot E_N \cdot E_{SS} \cdot S_N \cdot S_{SS} - k_{PR} \cdot E_N \cdot E_{SS} \cdot P_N \cdot P_{SS} \tag{12}$$

1.4 Normalisation of kinetic rates

Presumptions

- $k_{CN} = k_C \cdot E_{SS} \cdot S_{SS}$: normalised rate constant determining the formation of complex.
- $k_{CRN} = \frac{k_{CR} \cdot C_{SS}}{w}$: normalised rate constant determining the decomposition of complex.
- $k_{PN} = \frac{k_P \cdot C_{SS}}{w}$: normalized rate constant determining the product formation.
- $k_{PRN} = k_{PR} \cdot E_{SS} \cdot P_{SS}$: normalized rate constant determining the product decomposition.

Equations

$$S: 0 = \Phi_I(1-f) - k_{CN} \cdot E_N \cdot S_N + k_{CRN} \cdot C_N \tag{13}$$
$$C: 0 = k_{CN} \cdot E_N \cdot S_N + k_{PRN} \cdot E_N \cdot P_N - k_{PN} \cdot C_N - k_{CRN} \cdot C_N \tag{14}$$
$$P: 0 = k_{PN} \cdot C_N - \Phi_O - k_{PRN} \cdot E_N \cdot P_N \tag{15}$$
$$E: 0 = k_{PN} \cdot C_N + k_{CRN} \cdot C_N - k_{CN} \cdot E_N \cdot S_N - k_{PRN} \cdot E_N \cdot P_N \tag{16}$$

1.5 Introducing ratios of constants describing complex formation and dissociation

Presumptions

- $r_1 = \frac{k_{PRN}}{k_{CN}}$: ratio among backward and forward constants describing complex formation.
- $r_2 = \frac{k_{CRN}}{k_{PN}}$: ratio among backward and forward constants describing complex dissociation.

Equations

Substrate consumption (inserting r_1 and r_2 into Equation 13):

$$S: \ 0 = \Phi_I(1-f) - k_{CN} \cdot E_N \cdot S_N + r_2 \cdot k_{PN} \cdot C_N \tag{17}$$

Complex formation (inserting r_1 and r_2 into Equation 14):

$$C: \ 0 = k_{CN} \cdot E_N \cdot S_N + r_1 \cdot k_{CN} \cdot E_N \cdot P_N - k_{PN} \cdot C_N - r_2 \cdot k_{PN} \cdot C_N \tag{18}$$

1.6 Normalised steady state values equal 1

Presumptions

- $S_N = 1$
- $C_N = w$
- $E_N = 1$
- $P_N = 1$

Equations

Substrate consumption (inserting presumptions into Equation 17):

$$S: \ 0 = \Phi_I(1-f) - k_{CN} + r_2 \cdot k_{PN} \cdot w \tag{19}$$

Complex formation (inserting presumptions into Equation 18):

$$\begin{aligned} C: \ 0 &= k_{CN} + r_1 \cdot k_{CN} - k_{PN} \cdot w - r_2 \cdot k_{PN} \cdot w \\ &= k_{CN} \cdot (1 + r_1) - k_{PN} \cdot w \cdot (1 + r_2) \end{aligned} \tag{20}$$

1.7 Metabolic reactions tend to proceed in the forward direction

Presumptions

In undisturbed steady state reactions tend to proceed in the forward direction:

- $k_{CN} >> k_{PRN} \Rightarrow r_1 << 1$
- $k_{PN} >> k_{CRN} \Rightarrow r_2 << 1$

Flux towards complex formation and complex dissociation is the same:

- $r_1 = r_2 = r$

Equations

Complex formation (assuming $r << 1 \approx 0$ in Equation 20):

$$C: \ k_{CN} \cdot (1+0) = k_{PN} \cdot w \cdot (1+0) \Rightarrow k_{CN} = k_{PN} \cdot w \tag{21}$$

Substrate consumption (inserting $k_{CN} = k_{PN} \cdot w$ into Equation 19):

$$S: \ 0 = \Phi_I(1-f) - k_{PN} \cdot w + r \cdot k_{PN} \cdot w \Rightarrow k_{PN} = \frac{\Phi_I(1-f)}{w(1-r)} \tag{22}$$

1.8 Expressing normalised reaction constants

Presumptions

- $k_{PN} = \frac{\Phi_I(1-f)}{w(1-r)}$ (see Equation 22)
- $r_1 = r = \frac{k_{PRN}}{k_{CN}}$ (see Introducing ratios of constants describing complex formation and dissociation)
- $r_2 = r = \frac{k_{CRN}}{k_{PN}}$ (see Introducing ratios of constants describing complex formation and dissociation)
- $k_{CN} = k_{PN} \cdot w$ (see Equation 21)

Equations 1

$$k_{PN} = \frac{\Phi_I(1-f)}{w(1-r)} \tag{23}$$

$$k_{CRN} = \frac{r \cdot \Phi_I(1-f)}{w(1-r)} \tag{24}$$

$$k_{CN} = \frac{\Phi_I(1-f)}{(1-r)} \tag{25}$$

$$k_{PRN} = \frac{r \cdot \Phi_I(1-f)}{(1-r)} \tag{26}$$

Parameter interpretation is as follows:

- r: reversibility of the reaction,
- Φ_I: metabolic influx into the reaction,

- f: proportion of flux into alternative pathways,
- w: ratio between the rate of complex formation and product formation – ratio between bound and free enzyme in steady state ($w = \frac{C_{SS}}{E_{SS}}$) - $w \approx 1$ in the reactions tending to move in the forward direction in the steady state (as is the case of metabolic networks). Since the concentrations are normalised according to the enzyme concentration in steady state (E_{SS}), w should equal the complex concentration in the steady state (C_{SS}).

Equations 2

Inserting normalised reaction constants into product formation equation in normalised steady state (see Equation 15) yields

$$\begin{aligned} P: 0 &= \frac{\Phi_I(1-f)}{w(1-r)} \cdot C_N - \Phi_O - \frac{r \cdot \Phi_I(1-f)}{(1-r)} \cdot E_N \cdot P_N \\ \Phi_O &= \Phi_I(1-f) \\ C_N &= w(1-r)\left(1 - \frac{r}{1-r} \cdot E_N \cdot P_N\right) = w\left(1 - r(1 - E_N \cdot P_N)\right) \end{aligned} \tag{27}$$

Inserting normalised reaction constants into equation governing enzyme dynamics in normalised steady state (see Equation 16) yields

$$\begin{aligned} E: 0 &= \frac{\Phi_I(1-f)}{w(1-r)} \cdot C_N + \frac{r \cdot \Phi_I(1-f)}{w(1-r)} \cdot C_N - \\ &- \frac{\Phi_I(1-f)}{(1-r)} \cdot E_N \cdot S_N - \frac{r \cdot \Phi_I(1-f)}{(1-r)} \cdot E_N \cdot P_N \\ 0 &= \frac{1}{w} \cdot C_N + \frac{r}{w} \cdot C_N - E_N \cdot S_N - r \cdot E_N \cdot P_N \\ 0 &= \frac{1+r}{w} \cdot C_N - E_N \cdot S_N - r \cdot E_N \cdot P_N \\ 0 &= \frac{1+r}{w} \cdot w\left(1 - r(1 - E_N \cdot P_N)\right) - E_N \cdot S_N - r \cdot E_N \cdot P_N \\ 0 &= (1+r)(1 - r + r \cdot E_N \cdot P_N) - E_N \cdot S_N - r \cdot E_N \cdot P_N \\ 0 &= 1 - r + r \cdot E_N \cdot P_N + r - r^2 + r^2 \cdot E_N \cdot P_N - E_N \cdot S_N - r \cdot E_N \cdot P_N \\ 0 &= 1 - r^2 + r^2 \cdot E_N \cdot P_N - E_N \cdot S_N \\ S_N &= \frac{1 - r^2}{E_N} + r^2 \cdot P_N \end{aligned} \tag{28}$$

2 Brief documentation of `SysBio` library

2.1 Enzyme catalysed reaction `ESReaction`

Description of `ESReaction` `Modelica` object class (see Figure 2).

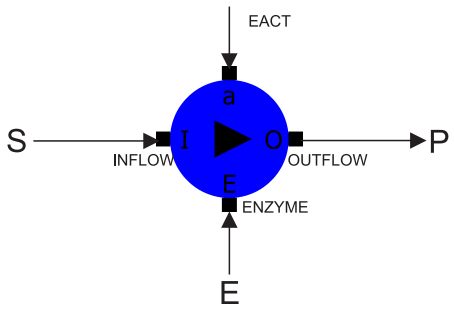

Figure 2: `ESReaction` `Modelica` object class with explicit labelling of its connectors.

Connectors

- $INFLOW$: substrate inflow (S),
- $ENZYME$: enzyme inflow (E),
- $OUTFLOW$: product outflow (P),
- $EACT$: regulator of enzyme activity (optional).

Parameters

- k_C: complex formation constant (calculated from initial conditions),
- k_P: product formation constant (calculated from initial conditions),
- r: reversibility of the reactions (user defined, default value set to 0.01):
  - note: the label w is used for this parameter in the Modelica code;
  - 0: irreversible;
  - 1: reversible.
  - An interesting situation occurs if all the reactions in the network are reversible. In this case, the unique calculation of the model states after perturbation is not possible as the system has an infinte number of solutions. However, in most metabolic networks irreversible reactions also occur, at the latest, when a metabolite is eliminated from an organism [Belič et al., 2013].

- $Q_0 = w$: initial (steady state) complex concentration (the default value set to 0.01).
- $M = 1$: number of substrate molecules consumed in one reaction (user defined, default value set to 1);

Variables

- Q: complex concentration.

Presumptions

- $k_{CR} = r \cdot k_P$,
- $k_{PR} = r \cdot k_c$.

Equations

If connector $EACT$ is connected, enzyme activity is proportional to its quantity:

$$e_{act} = \begin{cases} EACT.Q; & \text{if } EACT \text{ is connected,} \\ 1; & \text{else.} \end{cases} \tag{29}$$

Substrate consumption equals the amount of complex formation subtracted by complex dissociation:

$$\begin{aligned} S.FI = INFLOW.\Phi &= M * (e_{act} * k_C * S.Q^M * E.Q - k_{CR} * Q) \\ &= M * (e_{act} * k_C * S.Q^M * E.Q - r * k_P * Q) \end{aligned} \tag{30}$$

Product formation from the complex and product dissociation:

$$\begin{aligned} P.FI = -OUTFLOW.\Phi &= k_P * Q - e_{act} * k_{PR} * P.Q * E.Q \\ &= k_P * Q - e_{act} * r * k_C * P.Q * E.Q \end{aligned} \tag{31}$$

Change of complex concentrations:

$$\frac{dQ}{dt} = S.FI - P.FI = INFLOW.\Phi + OUTFLOW.\Phi \tag{32}$$

Amount of enzyme consumed is the same as the amount of complex formed:

$$E.FI = ENZYME.\Phi = \frac{dQ}{dt} = S.FI - P.FI \tag{33}$$

Notes

- Parameters k_C and k_P have the following definitions:
  ```
  parameter Real kC(fixed = false);
  parameter Real kP(fixed = false);
  ```
  This means that the values of parameters are implicitly calculated from the initial complex concentration:
  ```
  parameter Real Q0 = 0.01;
  Real Q(start = Q0, fixed = true);
  ```

- The only parameters that need to be known are initial complex concentration in steady state (Q_0, which equals w - see derivation) and reversibility of reactions r.
- Flux distribution is defined within the rest of the metabolic networks outside the object class `ESReaction`.

2.2 Substrate source `ESource`

The component defines the metabolic influx into the network. The metabolic influx is controlled by an enzyme and its activity (see Figure 3).

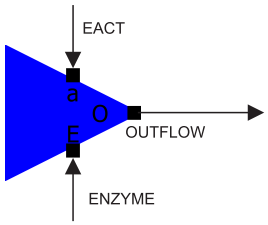

Figure 3: `ESource Modelica` object class with explicit labelling of its connectors.

Connectors

- $ENZYME$: enzyme inflow,
- $OUTFLOW$: substrate outflow,
- $EACT$: regulator of enzyme activity (optional).

Parameters

- k_C: complex formation constant (default value set to 1),
- k_P: substrate formation constant (calculated from initial complex concentration),
- $Q_0 = w$: initial complex concentration (default value set to 0.01).

Variables

- Q: complex concentration.

Equations

Enzyme activity connector defines the activity of enzyme only in the case it is connected. In this case E_{act} is set to the concentration on the connector. Otherwise, E_{act} is set to 1:

$$e_{act} = \begin{cases} EACT.Q; & \text{if } EACT \text{ is connected,} \\ 1; & \text{else.} \end{cases} \tag{34}$$

Substrate outflow equals complex concentration multiplied by substrate formation constant:

$$OUTFLOW.\Phi = -k_P * Q. \tag{35}$$

Change of complex concentration equals its production minus substrate outflow:

$$\frac{dQ}{dt} = e_{act} * k_C * E.Q + OUTFLOW.\Phi. \tag{36}$$

Enzyme consumption equals the change of complex concentration

$$ENZYME.\Phi = \frac{dQ}{dt}. \tag{37}$$

2.3 Substrate source `Source`

Object class `Source` describes flow of substrate mass and supports flow perturbations after predefined time (see Figure 4).

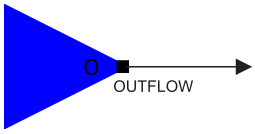

Figure 4: `Source Modelica` object class with explicit labelling of its connectors.

Connectors

- $OUTFLOW$: substrate outflow.

Parameters

- $massflow_1$: massflow before perturbation (default value set to 1),
- $massflow_2$: massflow after perturbation (default value set to 1),
- $switchtime$: time of perturbation (default value set to 1).

Equations

$$OUTFLOW.\Phi = \begin{cases} -massflow_1; & \text{if } t \leq switchtime, \\ -massflow_2; & \text{else} \end{cases} \tag{38}$$

2.4 Compound `Metabolite`

The `Modelica` object class `Metabolite` is presented in Figure 5. The object class does not include metabolite degradation.

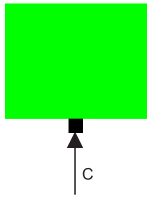

Figure 5: `Metabolite Modelica` object class with explicit labelling of its connectors.

Connectors

- C: metabolite inflow,

Parameters

- Q_0: initial metabolite concentration (default value set 1).

Variables

- Q: metabolite concentration.

Equations

Change of metabolite concentration:

$$\frac{dQ}{dt} = \begin{cases} 0; & \text{if } Q \leq 0 \text{ and } C.\Phi < 0, \\ C.\Phi; & \text{else.} \end{cases} \tag{39}$$

Connector concentration equals metabolite concentration

$$C.Q = Q. \tag{40}$$

2.5 Compound `Enzyme`

The `Modelica` object class `Enzyme` is presented in Figure 6. The object class includes enzyme degradation, which can be perturbed after predefined time.

Connectors

- C: enzyme inflow,

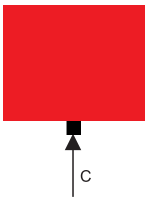

Figure 6: `Enzyme Modelica` object class with explicit labelling of its connectors.

Parameters

- Q_0: initial enzyme concentration (default value set to 1),
- $k1$, $k2$: parameters describing enzyme degradation constant (default values set to: $k_1 = 0.01, k_2 = 0$),
- *switchtime*: time of degradation constant perturbation (default value set to 0).

Variables

- Q: enzyme concentration.

Equations

Calculation of degradation constant:

$$k = \begin{cases} k1; & \text{if } t \leq switchtime, \\ k1 * \frac{1}{1+k2}; & \text{else.} \end{cases} \tag{41}$$

Change of enzyme concentration:

$$\frac{dQ}{dt} = \begin{cases} 0; & \text{if } Q \leq 0 \text{ and } C.\Phi - k * Q < 0, \\ C.\Phi - k * Q; & \text{else.} \end{cases} \tag{42}$$

Connector concentration equals enzyme concentration

$$C.Q = Q. \tag{43}$$

2.6 Compound `Protein`

The `Modelica` object class of (non-enzymatic) protein is presented in Figure 7. It includes almost the same description as `Enzyme` object class and differs only in initial parameter values:

- Q_0: initial protein concentration (default value set to 0),
- $k1$, $k2$: parameters describing protein degradation constant (default values set to: $k_1 = 0, k_2 = 0$),

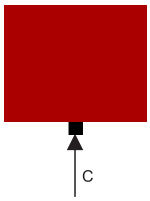

Figure 7: `Protein Modelica` object class with explicit labelling of its connectors.

- *switchtime*: time of degradation constant perturbation (default value set to 0).

2.7 Compound `mRNA`

The `Modelica` object class `mRNA` describing mRNA compound is presented in Figure 8. Object class `mRNA` again has the same description as `Enzyme` and

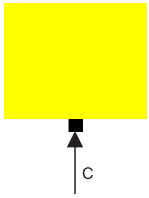

Figure 8: `mRNA Modelica` object class with explicit labelling of its connectors.

`Protein` object class, with the exception of initial parameter values:

- Q_0: initial mRNA concentration (default value set to 1),
- $k1$, $k2$: parameters describing mRNA degradation constant (default values set to: $k_1 = 0, k_2 = 0$),
- *switchtime*: time of degradation constant perturbation (default value set to 0).

2.8 Modeling transcription with `GeneExpressionControl_positive`

Gene expression is modelled with sigmoid functions. Transcription object classes monitor the concentration of the regulator (Q_C), which is in absence of regulator set to 1. Regulator consumption in the object class equals 0 (input flux is set to 0). The object class describing positive gene expression control is presented in Figure 9.

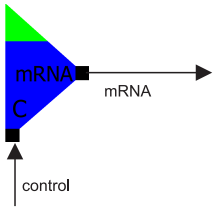

Figure 9: `GeneExpressionControl_positive Modelica` object class with explicit labelling of its connectors.

Connectors

- $mRNA$: mRNA outflow,
- *control*: control connector, where quantity of connected compound regulates the mRNA outflow (optional).

Parameters

- Φ_0: initial outflux of the transcription and influx into the mRNA component (default value set to 0.0001, arbitrary value),
- Q_{max}: maximum fold change of mRNA concentration (default value set to 5),
- Q_{Cmax}: sensitivity of gene expression to the regulator - maximum concentration of the regulator that results in the maximum fold-change in mRNA expression (default value set to 50).

Equations

$$K_{mRNA} = \frac{a * control.Q}{b + control.Q}, \tag{44}$$

where $a = \Phi_0 * (1 + b)$ and $b = \frac{Q_{Cmax} * (Q_{max} - 1)}{Q_{Cmax} - Q_{max}}$. With the substitution of parameters, K_{mRNA} equals

$$K_{mRNA} = \frac{0.0005 * control.Q}{4.4 + control.Q}. \tag{45}$$

Outflow of mRNA therefore equals:

$$mRNA.\Phi = -K_{mRNA}. \tag{46}$$

2.9 Modeling transcription with `GeneExpressionControl_negative`

The object class describing negative gene expression control is presented in Figure 10. Object class is very similar to positive regulation as can be seen

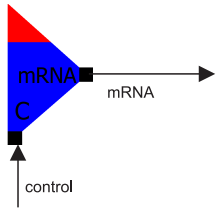

Figure 10: `GeneExpressionControl_negative` Modelica object class with explicit labelling of its connectors.

below.

Connectors

- $mRNA$: mRNA outflow,
- *control*: control connector, where quantity of connected compound regulates the mRNA outflow (optional).

Parameters

- Φ_0: initial outflux of the transcription and influx into the mRNA component (default value set to 0.0001, arbitrary value)
- Q_{max}: maximum fold change of mRNA concentration (default value set to 5)

Equations

$$K_{mRNA} = \frac{a * b}{b + control.Q}, \tag{47}$$

where $a = \frac{Q_{max} * \Phi_0}{b + control.Q}$ and $b = Q_{max} - 1$. With the substitution of parameters, K_{mRNA} equals

$$K_{mRNA} = \frac{0.0005}{4 + control.Q}. \tag{48}$$

Outflow of mRNA therefore equals:

$$mRNA.\Phi = -K_{mRNA}. \tag{49}$$

2.10 Modeling transcription with `GeneExpressionControl_lin`

The object class describing positive linear gene expression control is presented in Figure 11. Object class is a linear version of positive gene expression regulation

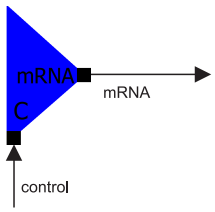

Figure 11: `GeneExpressionControl_lin` `Modelica` object class with explicit labelling of its connectors.

as can be seen below.

Connectors

- $mRNA$: mRNA outflow,
- *control*: control connector, where quantity of connected compound regulates the mRNA outflow (optional).

Parameters

- k: expression constant (default value set to 0.00001).

Equations

Outflow of mRNA is linearly proportional to concentration of control species (if control connector is not connected, concentration is set to value 1):

$$mRNA.\Phi = \begin{cases} -k * control.Q; & \text{if } control \text{ is connected,} \\ -k; & \text{else.} \end{cases} \tag{50}$$

2.11 Modelling translation with `EFormation_lin`

Translation describes intermediate reaction between mRNA and enzymatic (or non-enzymatic) protein and is implemented within the `Modelica` object class `EFormation_lin` (see Figure 12).

Connectors

- $INFLOW$: mRNA inflow,
- $OUTFLOW$: enzymatic or non-enzymatic protein outflow.

Figure 12: `EFormation_lin Modelica` object class with explicit labelling of its connectors.

Parameters

- k: translation constant (default value set to 0.01).

Equations

Object class does not consume any mRNA (it merely detects its quantity):

$$INFLOW.\Phi = 0. \tag{51}$$

Protein outflow equals translation constant multiplied by mRNA concentration:

$$OUTFLOW.\Phi = -k * INFLOW.Q. \tag{52}$$

2.12 Modelling protein activation with `Activation`

`SysBio` library supports post-translational activation or inhibition of proteins with two object classes, namely `Activation` and `Inhibition`. Both object classes can have up to five regulator ports, which correspond to activators or inhibitors. Their concentrations are only sensed by the object classes and are thus not consumed. The object class describing protein activation is presented in Figure 13.

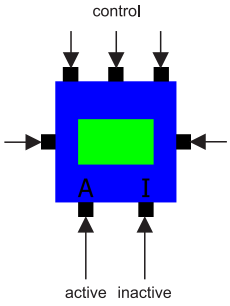

Figure 13: `Activation Modelica` object class with explicit labelling of its connectors.

Connectors

- *active*: active form of compound,
- *inactive*: inactive form of compound,
- *control*: five control connectors labeled with $control_1$, $control_2$, $control_3$, $control_4$ and $control_5$ (all are optional).

Parameters

- k_1, k_2, k_3, k_4, k_5: activation constants associated to each of the control connectors (default value set to 1),
- $Q_{10}, Q_{20}, Q_{30}, Q_{40}, Q_{50}$: normalisation constant for each of the control connectors (default value set to 1),
- k_a, k_i: define the ratio between activation and inhibition (default values are $k_a = 50$ and $k_i = 1$),
- Φ_{00}: determines the concentration of the active and inactive protein; if protein is regulated by both object classes, Φ_{00} should be set to 0; otherwise it should be set to 0.01, to prevent the accumulation of the active or inactive protein. In this case k in translation object class should be set to 0.02.

Equations

Influx of inactive protein

$$inactive.\Phi = k_i * inactive.Q * Q_c - k_a * active.Q - \Phi_{00} \tag{53}$$

and influx of active protein

$$active.\Phi = -inactive.\Phi, \tag{54}$$

where

$$Q_c = \frac{\frac{k_1 * control_1.Q}{Q_{10}} + \frac{k_2 * control_2.Q}{Q_{20}} + \frac{k_3 * control_3.Q}{Q_{30}} + \frac{k_4 * control_4.Q}{Q_{40}} + \frac{k_5 * control_5.Q}{Q_{50}}}{k_1 + k_2 + k_3 + k_4 + k_5}. \tag{55}$$

Here only the parts of the equation that are associated to the connectors being use are taken into account (i.e. k_i-s for connectors that are not used are set to zero).

2.13 Modelling protein inhibition with `Inhibition`

The object class describing post-translational protein inhibition is presented in Figure 14. It uses the same parameters and connectors as `Activation` object

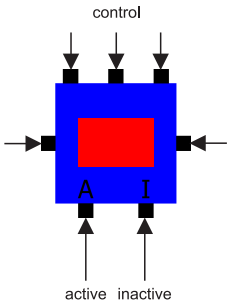

Figure 14: `Inhibition Modelica` object class with explicit labelling of its connectors.

class. The only difference is in the equations defining fluxes of active and inactive proteins. Influx of inactive protein is thus

$$inactive.\Phi = k_i * inactive.Q - k_a * active.Q * Q_c - \Phi_{00} \tag{56}$$

and influx of active protein

$$active.\Phi = -inactive.\Phi. \tag{57}$$

3 Equations and figures for the IBD4Health

Enzyme catalysed reaction figure (Figure 15).

$$\mathrm{E} + \mathrm{S} \underset{\mathrm{k_{CR}}}{\overset{\mathrm{k_C}}{\rightleftharpoons}} \mathrm{C} \underset{\mathrm{k_{PR}}}{\overset{\mathrm{k_P}}{\rightleftharpoons}} \mathrm{P} + \mathrm{E}$$

Figure 15: Enzyme catalysed reaction according to Michaelis-Menten kinetic formalism.

3.1 Basic ODE description

$$\frac{dS}{dt} = -k_C \cdot E \cdot S + k_{CR} \cdot C \tag{58}$$

$$\frac{dC}{dt} = k_C \cdot E \cdot S + k_{PR} \cdot E \cdot P - k_P \cdot C - k_{CR} \cdot C \tag{59}$$

$$\frac{dP}{dt} = k_P \cdot C - k_{PR} \cdot E \cdot P \tag{60}$$

$$\frac{dE}{dt} = k_P \cdot C + k_{CR} \cdot C - k_C \cdot E \cdot S - k_{PR} \cdot E \cdot P \tag{61}$$

3.2 Steady state presumption

$$S_N = \frac{S}{S_{SS}} = 1$$

$$C_N = \frac{C}{E_{SS}} = w$$

$$E_N = \frac{E}{E_{SS}} = 1$$

$$P_N = \frac{P}{P_{SS}} = 1$$

$$r_1 = \frac{k_{PR}}{k_C}$$

$$r_2 = \frac{k_{CR}}{k_P}$$

$$k_C >> k_{PR} \Rightarrow r_1 << 1$$

$$k_P >> k_{CR} \Rightarrow r_2 << 1$$

$$r_1 = r_2 = r$$

$$r = \frac{k_{PR}}{k_C} = \frac{k_{CR}}{k_P}$$
$$k_{PR} = k_C \cdot r$$
$$k_{CR} = k_P \cdot r$$

3.3 Simplified ODE description

$$\frac{dS}{dt} = -k_C \cdot E \cdot S + r \cdot k_P \cdot C \tag{62}$$
$$\frac{dC}{dt} = k_C \cdot E \cdot S + r \cdot k_C \cdot E \cdot P - k_P \cdot C - r \cdot k_P \cdot C \tag{63}$$
$$\frac{dP}{dt} = k_P \cdot C - k_C \cdot r \cdot E \cdot P \tag{64}$$
$$\frac{dE}{dt} = k_P \cdot C + k_P \cdot r \cdot C - k_C \cdot E \cdot S - k_C \cdot r \cdot E \cdot P \tag{65}$$

References

[Belič et al., 2013] Belič, A., Ačimović, J., Naik, A., and Goličnik, M. (2013). Analysis of the steady-state relations and control-algorithm characterisation in a mathematical model of cholesterol biosynthesis. *Simulation Modelling Practice and Theory*, 33:18–27.

[Naik, 2013] Naik, A. (2013). *Construction of SteatoNet: A metabolic network to investigate NAFLD-related hepatic steatosis*. PhD thesis, Ebhard-Karls University of Tuebingen, Tuebingen, Germany.

[Naik et al., 2014] Naik, A., Rozman, D., and Belič, A. (2014). SteatoNet: The first integrated human metabolic model with multi-layered regulation to investigate liver-associated pathologies. *PLOS Computational Biology*, 10(12):e1003993.