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ON THE NUMERICAL SOLUTION OF THE GENERAL "LIGAND–GATED NEURORECEPTORS MODEL" VIA CAS MATHEMATICA

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We present a software module for analysis of the *general "ligand–gated neuroreceptors model" (GLGNM)* within the programming environment of CAS *Mathematica*. Numerical examples which demonstrate scientific applications and visualization properties of the module are presented.

1. Introduction

Consider the network for "ligand–gated neureceptors model" [1], [2]:

(1)
$$\begin{gathered}
C_0 \underset{k_u}{\overset{2k_bT}{\rightleftarrows}} C_1 \underset{k_{uDs}}{\overset{k_{Ds}}{\rightleftarrows}} D_s \\
C_1 \underset{2k_u}{\overset{k_bT}{\rightleftarrows}} C_2 \underset{k_{uDf}}{\overset{k_{Df}}{\rightleftarrows}} D_f \\
D_s \underset{k_{fs}}{\overset{k_{sf}T}{\rightleftarrows}} D_f \\
C_1 \underset{k_{c1}}{\overset{k_{01}}{\rightleftarrows}} O_1 \\
C_2 \underset{k_{c2}}{\overset{k_{02}}{\rightleftarrows}} O_2
\end{gathered}$$

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with given transition rates: k_b, k_u, k_{uDs}, k_{Ds}, k_{c1}, k_{01}, k_{c2}, k_{02}, k_{uDf}, k_{Df}, k_{fs} and k_{sf}.

In this model, there is the unbound receptor form C_0, singly and doubly bound receptor forms C_1, C_2, slow and fast desensitized states D_s, D_f, and singly open and doubly open receptor forms O_1, O_2.

Variable T represents neurotransmitter concentration. The model is the most abundant inhibitory neutransmitter in the human brain [3].

If all transition rates are described by mass action kinetics, we obtain the following system of differential equations [2]:

$$
\begin{aligned}
C_0'(t) &= -2k_bC_0T + k_uC_1 \\
C_1'(t) &= 2k_bC_0T - k_uC_1 + k_{uDs}D_s - k_{Ds}C_1 + 2k_uC_2 - k_bC_1T + \\
&\quad k_{c1}O_1 - k_{01}C_1 \\
C_2'(t) &= k_bC_1T - 2k_uC_2 + k_{c2}O_2 - k_{02}C_2 + k_{uDf}D_f - k_{Df}C_2 \\
D_s'(t) &= k_{fs}D_f - k_{sf}D_sT + k_{Ds}C_1 - k_{uDs}D_s \\
D_f'(t) &= k_{sf}D_sT - k_{fs}D_f + k_{Df}C_2 - k_{uDf}D_f \\
O_1'(t) &= k_{01}C_1 - k_{c1}O_1 \\
O_2'(t) &= k_{02}C_2 - k_{c2}O_2 \\
T'(t) &= k_uC_1 - 2k_bC_0T + 2k_uC_2 - k_bC_1T + k_{fs}D_f - k_{sf}D_sT.
\end{aligned}
\tag{2}
$$

2. Main results

Consider the general network ($n = 2, 3, \ldots$) for "ligand–gated neureceptors model" (GLGNM):

$$
\begin{gathered}
C_0 \rightleftarrows C_1 \rightleftarrows D_1 \\
\ldots \\
C_{n-1} \rightleftarrows C_n \rightleftarrows D_n \\
D_1 \rightleftarrows D_2 \\
\ldots \\
D_{n-1} \rightleftarrows D_n \\
C_1 \rightleftarrows O_1 \\
\ldots \\
C_n \rightleftarrows O_n
\end{gathered}
\tag{3}
$$

with given transition rates.

In this model, there is the unbound receptor form C_0, singly and doubly bound receptor forms $C_1, \ldots, C_n$, slow and fast desensitized states $D_1, \ldots, D_n$, and singly open and doubly open receptor forms $O_1, \ldots, O_n$.

2.1. The model of the (GLGNM) studied via the programming environment *Mathematica*

A *CAS Mathematica* software module has been developed (intellectual property) for studying the (GLGNM) (3).

The software module offers the following possibilities:

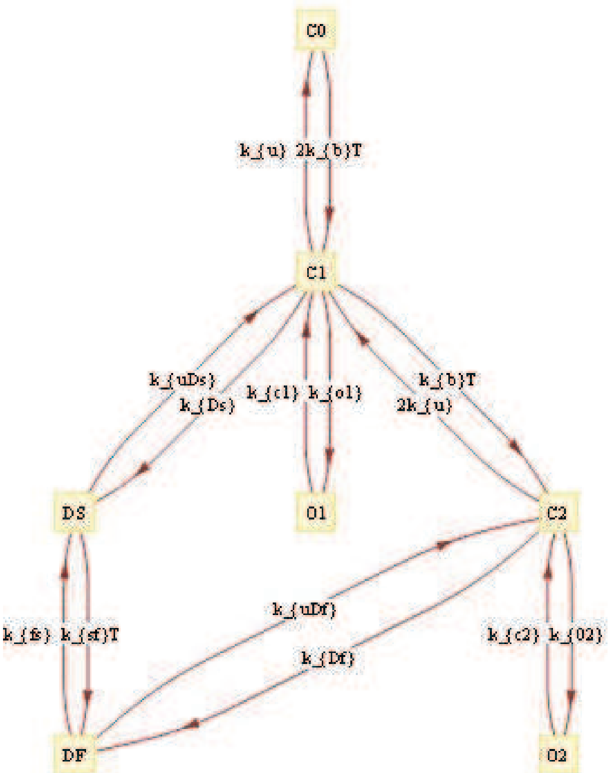

Figure 1: Bipartite graph of the kinetic "ligand–gated neureceptors" model via programming environment *CAS Mathematica*

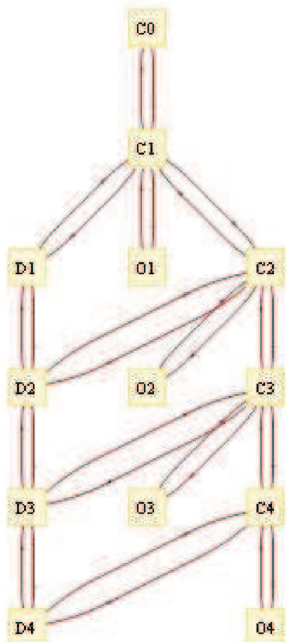

Figure 2: The case $n = 4$

i) generation of a general network (3) for a given (by the user) arbitrary transition rates;
ii) generation and explicite presentation of the differential mass action equations for the mechanism;
iii) visualisation of the solutions of the dynamical system of differential equations as functions of the time t;
iv) generation and visualization of the bipartite digraph [5] of the general kinetic "ligand–gated neureceptors" model;
v) visualization of the variable $T(t)$ – present neurotransmitter concentration;
vi) visualization of the open state concentration solution, $O_1(t) + O_2(t) + \cdots + O_n(t)$ of the general kinetic "ligand–gated neureceptors" model;
vii) visualization of the desensitized: $D_1(t) + D_2(t) + \cdots + D_n(t)$ of the general kinetic "ligand–gated neureceptors" model;
viii) visualization of the closed bound: $C_1(t) + C_2(t) + \cdots + C_n(t)$ of the general kinetic "ligand–gated neureceptors" model;
ix) sensitive analysis of the system of differential equations, etc.

2.2. Experiments via the programming environment *Mathematica*

The test provided on our control example with transition rates: $k_b = 5000000$, $k_u = 131$, $k_{uDs} = 0.2$, $k_{Ds} = 13$, $k_{c1} = 1100$, $k_{01} = 200$, $k_{c2} = 142$, $k_{02} = 2500$, $k_{uDf} = 25$, $k_{Df} = 1250$, $k_{fs} = 0.01$ and $k_{sf} = 2$ [8] and initial conditions:$C_0(0) = 0$, $C_1(0) = 0.1$, $C_2(0) = 0.2$, $DS_1(0) = 0.05$, $DF_1(0) = 0.06$, $O_1(0) = 0.2$,

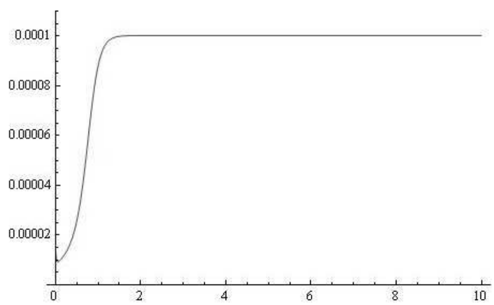

Figure 3: The variable $T(t)$ – present neurotransmitter concentration. We note that $T(t)$ represent typical sigmoid function [6], [7]

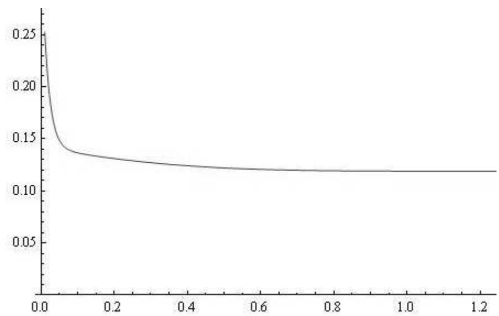

Figure 4: Open state concentration solution, $O_1(t) + O_2(t)$

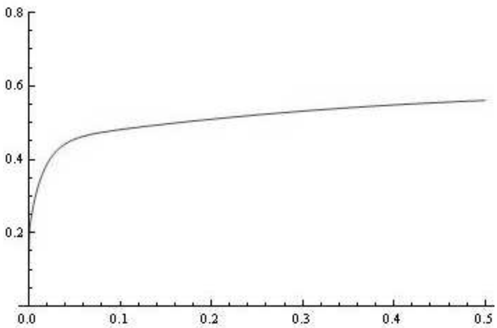

Figure 5: Desensitized: $D_s(t) + D_f(t)$

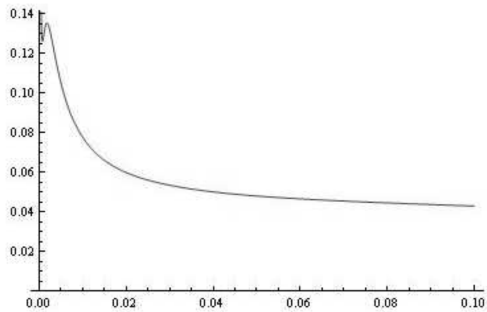

Figure 6: Closed bound: $C_1(t) + C_2(t)$

$O_2(0) = 0.1$ and $T(0) = 0.1$ is plotted on Figure 3 (the variable $T(t)$ – present neurotransmitter concentration).

The oppen state concentration solution, $O_1(t) + O_2(t)$ for the model (3) is plotted on Figure 4.

Figure 5 displays the desensitized: $D_s(t) + D_f(t)$.

The closed bound: $C_1(t) + C_2(t)$ is plotted on Figure 6.

The corresponding bipartite digraph of the mechanism (3) is shown in Figure 1 (see, also Figure 2 for the case $n = 4$).

3. Conclusion remarks

The demonstrated module presents a natural upgrade of *CAS Mathematica*.

From these experiments it has been possible to construct detailed kinetic schemes describing transitions to and from multiple receptors states.

We note that at each step the program exercise control over the computational errors combined with super–sensitive analysis on the differential kinetic equations.

The case of first order reactions when every two distinct components interact reversibly between themselves is considered in [4].

For some related software products implemented in software environments other than *CAS Mathematica*, see [1], [2], [9]–[11].

We shall expressively note that for large values of n the problem for the presentation of the time–course solution of the differential system is very tedious [14].

In many cases the solution's amplitude for neurotransmitter concentration is very small (see Fig. 3), which complicates the visualization of the solutions.

In order to avoid this visualization problem, another function of our module is to authomatically regulate the monitor and plotting charcteristics.

We note that at each step the program exercises control over the computational errors. The control is partially accomplished by using the well-known operators AccuracyGoal, PrecisionGoal and WorkingPrecision.

At any case the computational results produced by the proposed Mathematica module offered in the paper are reliable.

The approximation of the interval step function by the logistic and other sigmoid functions is discussed from various approximation, computational and modelling aspects in [15]–[26].

Appendix. AMPA neuroreceptor model

Consider the network for "ligand–gated AMPA neureceptors model" (GLGANM) [12], [13]:

$$\begin{array}{c} C_0 \underset{k_{u1}}{\overset{k_b T}{\rightleftarrows}} C_1 \underset{k_{ud}}{\overset{k_d}{\rightleftarrows}} D_1 \\ C_1 \underset{k_{u2}}{\overset{k_b T}{\rightleftarrows}} C_2 \underset{k_{ud}}{\overset{k_d}{\rightleftarrows}} D_2 \\ C_2 \underset{k_c}{\overset{k_0}{\rightleftarrows}} O \end{array} \tag{4}$$

with given transition rates: k_b, k_0, k_c, k_{u1}, k_{u2}, k_d and k_{ud}.

In this model, there is the unbound receptor form C_0, singly and doubly bound receptor forms C_1, C_2, which can lead to desensitized states D_1, D_f, respectively, and the open receptor form O.

Variable T represents neurotransmitter concentration.

If all transition rates are described by mass action kinetics, we obtain the following system of differential equations [2]:

$$\begin{aligned} C_0'(t) &= -k_b C_0 T + k_{u1} C_1 \\ C_1'(t) &= k_b C_0 T - k_{u1} C_1 + k_{ud} D_1 + k_{u2} C_2 - k_b C_1 T - k_d C_1 \\ C_2'(t) &= k_b C_1 T - k_{u2} C_2 + k_c O - k_0 C_2 + k_{ud} D_2 - k_d C_2 \\ D_1'(t) &= k_d C_1 - k_{ud} D_1 \\ D_2'(t) &= k_d C_2 - k_{ud} D_2 \\ O'(t) &= k_0 C_2 - k_c O \\ T'(t) &= k_{u1} C_1 - k_b C_0 T + k_{u2} C_2 - k_b C_1 T. \end{aligned} \tag{5}$$

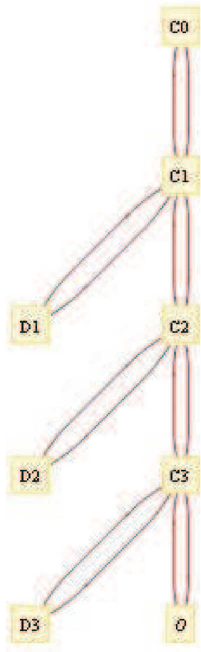

Figure 7: The case $n = 3$ for the "ligand–gated AMPA neureceptors model" – (GLGANM)

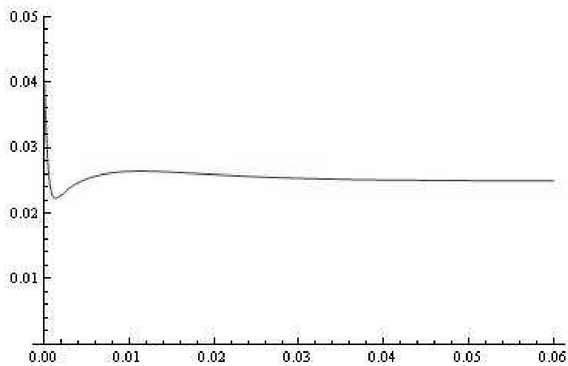

Figure 8: The variable $T(t)$ – present neurotransmitter concentration for the "ligand–gated AMPA neureceptors model" – (GLGANM)

Consider the general network ($n = 2, 3, \ldots$) for the "ligand–gated AMPA neureceptors model" – (GLGANM):

$$\begin{gathered} C_0 \rightleftarrows C_1 \rightleftarrows D_1 \\ \cdots \\ C_{n-1} \rightleftarrows C_n \rightleftarrows D_n \\ C_n \rightleftarrows O \end{gathered} \tag{6}$$

with given transition rates.

The test provided on our control example with transition rates: $k_b = 13000000$, $k_{u1} = 5.9$, $k_{ud} = 64$, $k_d = 900$, $k_c = 200$, $k_0 = 2700$ and $k_{u2} = 86000$ [13] and initial conditions:$C_0(0) = 0$, $C_1(0) = 0.1$, $C_2(0) = 0.2$, $D1(0) = 0.05$, $D2(0) = 0.06$, $O(0) = 0.2$, and $T(0) = 0.1$ is plotted on Figure 8 (the variable $T(t)$ – present neurotransmitter concentration for the "ligand–gated AMPA neureceptors model" - (GLGANM)).

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