Pitchfork bifurcation in a receptor theory-based model of the serotonergic system

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Abnormalities in the serotonergic system are thought to be a potent cause of several mental diseases. Past research has shown that autoreceptors are the key component. It is thought that the autoreceptor constructs a negative feedback circuit on this system and realizes homeostatic control on its neural activity. This study is mainly organized from the above mentioned knowledge. In this paper, we construct two possible models of the serotonergic system based on receptor theory and provide some predictions for this system with each model. In the first model, we predict that the deficit of serotonin synthesis causes destabilization of the amount of autoreceptors; autoreceptors show an explosive increase if serotonin synthesis drops below a certain threshold value. In the second model, we indicate that the serotonergic system changes its stable property from a monostable one to a bistable one by certain factors. We clarify these factors and show that this changing process is named pitch-fork bifurcation. Additionally, we also suggest another notable phenomena which would appear when we consider a stochastic perturbation on the receptor expressions. Lastly, we suggest some experimental ideas towards the verification of the validity of these models.

1 Introduction

Serotonin (5-HT) has attracted the attention of researchers as the pathophysiological factor of anxiety, mood disorders, suicide and others. Serotonergic systems are especially studied in association with the study of major depressive disorder:1 the hypothesis that focuses on the dysfunctions of monoamines (serotonin, 5-HT; dopamine, DA; norepinephrine, NE) is called the monoamine hypothesis.

In the monoamine hypothesis, serotonin deficiency in the brain is thought to be an important cause of depressive symptoms. A previous study has indicated that this deficiency is caused by a dysfunction in the serotonergic cells at the dorsal raphe nucleus (DRN).2 A lot of studies have increased the understanding of the morphology and the physiology of serotonergic cells: it is generally accepted that the internal mechanism of the serotonergic cell is associated with the following properties.3,4

1. A serotonergic cell releases serotonin to the extracellular area.
2. A serotonergic cell has an autoreceptor in its cell body membrane and a transporter at the axon terminals.
3. Serotonin–autoreceptor binding inhibits the serotonin release and the serotonin synthesis.
4. A serotonergic cell takes homeostatic control of itself by upregulating and downregulating autoreceptors and postsynaptic-receptors according to the amount of serotonin–receptor bindings.

In this paper, we predict some remarkable phenomena in the serotonergic system mainly using the above mentioned knowledge. To predict what occurs in this system, we especially focus on the structural stability. From the viewpoint of dynamical systems, past clinical study suggests the bistable property of major depressive disorder: a depressive patient moves back and forth between normalcy and syndrome during the treatment.5 Therefore, it is an important issue to analyse the structural stability of the serotonergic system.

The outline of this paper is as follows. At first, we construct a model of receptor dynamics. As we will see later, it is uniquely derived from the requirement of homeostatic control of the serotonergic cell. Second, we propose two dynamical models of the amount of extracellular serotonin, both of which satisfy the above mentioned properties. Then we analyse these structural stability and bifurcation parameters. Lastly, we suggest some experimental ideas to verify the validity of our models.

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2 Model construction

2.1 Theoretical basis

At first, we briefly introduce the receptor theory. Receptor theory is the theoretical basis of this study to model the receptor dynamics.

Receptor theory gives us the modelling technique for the dynamics of agonist–receptor binding. Let us express the amount of agonist as \([A]\), unbounded receptor as \([R]\) and complex as \([AR]\). In the receptor theory, the agonist–receptor interaction shown in eqn (1):

\[
[A] + [R] \xrightleftharpoons[k_2]{k_1} [AR]
\]

(1)
is expressed by a differential eqn (2):

\[
\frac{d[AR]}{dt} = k_1[A][R] - k_2[AR].
\]

(2)

where \(k_1\) is the binding reaction velocity and \(k_2\) is the unbinding reaction velocity. From eqn (2), we can derive the stable fixed point of this system as

\[
[AR] \xrightarrow{} \left(\frac{k_2}{k_1}\right)^{-1} [A][R].
\]

(3)

The ratio \(K_D = k_2/k_1\) is usually called the dissociation constant. A larger \(K_D\) indicates that the situation that the leftward reaction \([AR] \rightarrow [A] + [R]\) is dominant over the rightward reaction.

Receptor theory also gives us the modelling technique for the response effect of the agonist–receptor binding. This theory expresses the response effect as a monotonically increasing function of the amount of binding \([AR]\):6

\[
\text{Response} = f([AR]).
\]

(4)

Various types of the function \(f\) were proposed in the progress of receptor theory.7 For example, in the earliest work done by A. J. Clark,8 eqn (4) is expressed in the following manner:

\[
\text{Response} = [AR].
\]

(5)

In another case, which is called the operational model,9 eqn (4) is expressed empirically as:

\[
\text{Response} = \frac{[AR]}{[AR] + K_E} E_m
\]

(6)

where \(K_E\) is the parameter which reflects the properties of the tissue and agonist and \(E_m\) is the parameter which shows the maximal response of the tissue. As explained above, \(f\) is usually and empirically assumed to be a monotonically increasing function.

2.2 Modelling the serotonergic system

Let us consider the serotonergic system. DRN has a serotonergic neuron which is a major source of serotonin in the brain. Released serotonin widely affects the forebrain: the neocortex, the dorsal striatum, ventral striatum, and the amygdala.2

We define “serotonergic system” as the serotonergic neuron at the DRN, which releases serotonin, and receptive organs of serotonin.

Here are the definitions of the variables (they are also described in Fig. 1). The concentration of extracellular serotonin is expressed in \([S]\). The serotonergic system has an autoreceptor near the body of a cell, so the density of autoreceptors is expressed as \([R_A]\). The density of postsynaptic receptors is expressed as \([R_P]\). Extracellular serotonin binds to not only autoreceptors but also postsynaptic receptors at the postsynaptic cell, so the density of binding receptors is expressed as \([SR_{i=A,P}]\).

The relationship of these variables is summarized by the following scheme:

1. Presynaptic system

\[
[S] + [R_A] \xrightarrow{\text{SR}} [AR] \xrightarrow{\text{SR}} [SR_{A}]
\]

2. Postsynaptic system

\[
[S] + [R_P] \xrightarrow{\text{SR}} [SP] \xrightarrow{\text{SR}} [SR_{P}]
\]

Serotonin concentration \([S]\) is regulated by serotonin synthesis in serotonergic cells and the clearance effect by monoamine oxidase and serotonin transporters. Receptor density \([R_i]\) is regulated by receptor internalization in presynaptic cells and postsynaptic cells.

Our challenge is to model the dynamics of \([S], [R_A]\) and \([R_P]\) in a compelling way, as much as possible. As is shown in the following, the dynamics of both \([R_A]\) and \([R_P]\) are naturally derived from the requirement of homeostatic-controls for the effect of serotonin–autoreceptor binding \(f([SR_A])\) and for the effect of serotonin–postsynaptic receptor binding \(f([SR_P])\).

We employ below three assumptions:

1. Reaction velocity of serotonin–receptor binding (first equation) is sufficiently faster than that of receptor internalization.10,11 So we adopt \([SR_i] = K_i^{-1}[S][R_i]\); parameter \(K_i\) is the dissociation constant, so a lower \(K_i\) represents higher binding of serotonin and receptor.

2. The dynamics of \(K_i\) is slower than the dynamics of \([S]\) or \([R_i]\), enough to treat it as a constant parameter (exogenous variable),

...
This assumption is suggested by past studies in rats showing that chronic testosterone administration for two weeks increases the affinity of hippocampal 5-HT₁A receptors without changing the density of them.12,13 Although this result is not about the dorsal raphe nucleus, we assume a slow transition of the affinity of presynaptic and postsynaptic receptors in this analysis.

3. The dynamics of extracellular serotonin [S] is also sufficiently faster than that of receptor dynamics [Ri]. 14,15

It is known that the affinity of presynaptic receptors $K_A$ is reduced in a depressive state. 16 Lastly in this paper, we analyse the effect of $K_A$ and $K_R$ on the stability of this system.

In the model construction, we proceeded in two stages. At first, we constructed a model of receptor dynamics [RA] and [RP] based on receptor theory. Then we constructed two different models for serotonergic dynamics [S]; the reason why we propose two different models is due to the limited understanding of the internal mechanism of serotonergic cells. We tried to construct them in as careful a manner as possible.

2.2.1 Receptor dynamics. In this step, we will see that the receptor dynamics satisfies Davis’s criteria about the homeostatic control. 17 The dynamics near the equilibrium is uniquely determined to our suggested form without loss of generality.

At first, we derive the model of the autoreceptor dynamics [RA] and postsynaptic receptor dynamics [RP] near their equilibrium point. Then we constructed the model of the amount of external serotonin [S].

As noted in the introduction, we assume that the serotonergic cell somehow regulates itself to realize homeostatic control of the signal via autoreceptor-serotonin binding. We also assume that the postsynaptic cell regulates itself to realize homeostatic control of the signal via postsynaptic receptor-serotonin binding. It is also introduced that the response $f([SR])$ is a monotonically increasing function of [SR]. From this monotonicity, there exists one-to-one correspondence between $f([SR])$ and [SR]; homeostatic control on $f([SR])$ is equivalent to the fixed value control on [SR]. Thus we find that it is a necessary condition for the serotonergic system to take a fixed value control on [SR]. so the dynamics of the serotonergic system is uniquely determined in eqn (7):

$$\frac{1}{K_i} \frac{d[S][R_i]}{dt} = k_3 \left( \frac{H_i - 1}{K_i} - \frac{[S]}{[R_i]} \right) + \epsilon \left( \Delta_i^2 \right)$$

(7)

where $\Delta_i$ is the distance from the equilibrium ($\Delta_i = H_i - K^{-1}_i [S][R_i]$), $k_3$ is a time constant and $H_i$ is the target value of homeostatic control. Below we replace ($H_i = K^*H$) for convenience. We deform and approximate the left-hand side of eqn (7) as:

$$\frac{d[S][R_i]}{dt} = [S] \frac{d[R_i]}{dt} + [R_i] \frac{d[S]}{dt} \simeq [S] \frac{d[R_i]}{dt}$$

(8)

This approximation is justified because the time scale of serotonin generation or decomposition is faster than the dynamics of serotonin receptors. This type of system is known as a slow-fast system or a singular perturbed system. 18

Thus, we can transform the second line of eqn (7) as follows:

$$\frac{d[R_i]}{dt} = k_3 \left( \frac{H_i - 1}{K_i} - \frac{[S]}{[R_i]} \right) \quad \text{(with } [S] \neq 0).$$

(9)

Eqn (9) causes $[R_i] \rightarrow H_i$, which results in $[S][R_i] \rightarrow H_i$.

2.2.2 Serotonin dynamics

Model 1. Then we construct two different dynamical models which represent the dynamics of extracellular serotonin. It is important that the amount of serotonin is controlled by the effect from serotonin–autoreceptor binding [SR].

We construct the first model as follows:

$$\frac{d[S]}{dt} = k_4 (S_t - x[S][R_A] - [S])$$

(10)

where $S_t$ is a constant parameter which represents the synthesis of extracellular serotonin, which reflects serotonin release, synthesis and reuptake by the serotonergic cell. The second term expresses the inhibitory effect of serotonin–autoreceptor binding $f([SR])$. Receptor theory has proposed various types of $f([SR])$. In this study, for the sake of analytical convenience, we adopt the simplest form $f([SR]) = [SR]$. Then we get

$$\frac{d[S]}{dt} = k_4 \left( S_t - \frac{[S]}{[R_A]} \right) - [S])$$

(11)

where we replaced $K^{-1}_A = \beta$.

Approximately, we can replace $d[S]/dt = 0$ from the characteristics of its fast dynamics in comparison with receptor dynamics. Then, in this first model, the amount of extracellular serotonin is determined as follows at all time points:

$$[S] = \frac{S_0}{1 + \beta[R_A]}$$

(12)

We can see that this equation is the mono-decreasing function of $[R_A]$. This monotonous nature is consistent with our understanding of the characteristics of serotonin dynamics.

Model 2. We designed a second model to overcome the undesirable behavior of the first model.

In the first model, a subtle change in $[R_A]$ causes a most significant change in $[S]$, the less the autoreceptor expresses (i.e. $[R_A] \rightarrow 0$). In other words, it’s highly unlikely, but this model says that additional administration of the autoreceptor-inactivator would show its effect further and further whenever the autoreceptor is almost completely inactivated.

To overcome the above problem, we propose a second model as follows:

$$[S] = a + \frac{b}{1 + \exp (\eta (K^{-1}_A[R_A] - \lambda))}$$

(13)

The rate of change of $[S]$ becomes lower below the threshold $K^{-1}_A[R_A] = \lambda$. The parameters of the second model are almost comparable to that of the first model. Parameter $\eta$ modulates the impact of subtle change in $K^{-1}_A[R_A]$; it corresponds to parameter $\epsilon$. Parameter $b$ modulates the maximal value of $[S]$; it corresponds to parameter $S_t$. Parameter $a$ determines the lowest value of $[S]$; it was not included in the first model.
From the view point of these parameters, parameter $\lambda$ expresses the inflection point of the impact of serotonin-autoreceptor binding.

## 3 Analysis and results

### 3.1 Analysis on model 1

Thus the local model of the serotonergic system consists of eqn (7) and (11). We can contract this system as

$$
\begin{align*}
\frac{d[R_A]}{dt} &= k_3 \frac{H_A}{S_I^z} + \left(1 + \frac{H_A}{S_I^z}\right)[R_A], \quad \text{with } [S] \neq 0 \\
\frac{d[R_P]}{dt} &= k_3 \frac{H_P}{S_I^z} + \frac{H_P}{S_I^z} [R_A] - [R_P], \quad \text{with } [S] \neq 0
\end{align*}
$$

where we use $[S] = S_I(1 + z[R_A])^{-1}$. Because the stability of $[R_A]$ is not affected by any parameters, we focus our attention on the stability of $[R_A]$ below.

Under the condition $\frac{H_A}{S_I^z} = \frac{eH_A}{S_I^z} < 1$, we can derive the equilibrium point of this model as

$$
\begin{align*}
[R_A] &= \frac{K_A H_A}{S_I^z - eH_A} \\
[R_P] &= \frac{K_P H_P}{S_I^z - eH_A}
\end{align*}
$$

which satisfy $[R_A] > 0$ and $[R_P] > 0$. On the other hand, under the condition $\frac{eH_A}{S_I^z} > 1$, the equilibrium point diminishes because of emerging instability. Under this condition, dynamical eqn (14) becomes unstable and $[R_A]$ increases until $[S]$ goes to zero or $[R_A]$ becomes saturated.

To summarize the above analyses, it was indicated that $[R_A]$ becomes unstable if $S_I$ decreases below the threshold level $eH_A = S_I$; then $[R_A]$ would become saturated. Under the stable domain of $[R_A]$, our analyses also indicated that the equilibrium point of autoreceptors $[R_A] = 0$, it is sufficient to take a bifurcation analysis on the equilibrium point $R = a(H_A K_A)^{-1}[R_A]$.

$$
R = \left(1 + \frac{b'}{a} + \frac{1}{1 + \exp(\eta'(R - \lambda'))}\right)^{-1}
$$

where $b' = b/a$, $\eta' = H_A/a$, and $\lambda' = a\lambda/H_A$.

In this model, we employ numerical analysis, because it is difficult to solve eqn (19) algebraically which was shown in the first model. We examine the effect of three parameters $b'$, $\eta'$ and $\lambda'$ on the equilibrium point $R = a(H_A K_A)^{-1}[R_A]$.

Fig. 3 is an example of a bifurcation diagram which reflects the characteristics of eqn (18). This figure indicates that different bifurcation situations such as perfect/imperfect super critical pitch-fork bifurcation occurs in autoreceptor dynamics. Fig. 4 shows bifurcation diagrams of autoreceptor dynamics calculated by eqn (19). Although it is calculated in the specific parameter set, these figures clearly show that all of $b'$, $\eta'$ and $\lambda'$ work as bifurcation parameters. It is indicated that increasing $b'$ and increasing $\eta'$ tend to produce another stable point around low $R^*$ domain; then the original stable point diminishes as is shown in Fig. 3B. It is also shown that $b'$ and $\eta'$ causes bifurcation, but the number of equilibrium points doesn't diminish as is the case in $b'$ and $\lambda'$.

We didn't take a numerical bifurcation analysis on the dynamics of postsynaptic receptors $[R_P]$, because it is shown that $[S]$ is not a function of $[R_P]$; it is clear that $[R_P]$ doesn't show bifurcation phenomenon as far as we accept eqn (9). In fact, $[R_P]$ shows bifurcating behavior superficially, it is only affected by the bifurcation of $[R_A]$.

To summarize the above analysis, the second model predicted the occurrence of the supercritical pitch-fork bifurcation on the
dynamics of autoreceptors. It was also shown that $b_0$, $Z_0$, and $l_0$ play a role as bifurcation parameters in this bifurcation. Although the results of these analyses were only for $R$, these results are applicable to the dynamics of $[RA]$ qualitatively. It is because there exists the relationship $R = \frac{\alpha(H^A K^A)}{C_0^1 [RA]}$; the results of the analysis on $R$ is directly applicable by only multiplying a constant factor that doesn’t affect whether stability changes or not.

4 Discussion

In this study, we undertook a stability analysis on the two phenomenological models about the serotonergic system. In both cases, a decrease in serotonin synthesis changed the stability of the system and resulted in an increase of autoreceptor expression. Especially in the case of the second model, the bistability of serotonergic cells emerged through the supercritical pitch-fork bifurcation. In addition, we showed the bifurcation parameters which causes this bifurcation: $b'$, $\eta'$ and $\lambda'$. To return to the definition of these parameters, parameter $b'$ corresponds to serotonin synthesis, parameter $\eta'$ corresponds to the impact of serotonin–autoreceptor binding, and parameter $\lambda'$ corresponds to the inflection point of the impact of serotonin–autoreceptor binding (see eqn (13)).

We interpret these results as compared to the past findings on major depression. According to the second model, the serotonergic system emerges as a supercritical pitch-fork bifurcation through three parameters. Especially it is notable that the serotonergic system increases its vulnerability after bifurcation through $Z_0$: $[RA]$ cannot maintain its state stably in reaction to a perturbation on $b_0$ and $l_0$ (Fig. 4). The system moves back and forth between a stable manifold to the other. On the other hand, the serotonergic system doesn’t show such vulnerability before bifurcation occurs. This allows us to compare the pathology of major depression and bifurcation on the serotonergic system. Past clinical study suggests the bistable property of major depressive disorder: one is normalcy and the other is syndrome. Once a patient transits to syndrome, the patient holds on to this state tightly, and patient moves back and forth between normalcy and syndrome during the treatment. On the other hand, a healthy individual stably continues his normalcy state. Thus the second model can explain the characteristics of major depression. The following is another interpretation of the results of the second model. After the bifurcation through the parameter $\eta'$, the amount of receptor expression has two possibilities: high or low (Fig. 4). We think it reasonable to regard a higher amount of autoreceptor as a depressive state. It is known that a decrease of serotonin synthesis also occurs in major depression and that serotonin depletion (e.g. by treatment of mood disorders like MAO) causes a depressive state. In the second model,
serotonin depletion corresponds to the decrease of $b'$. As is shown in Fig. 4, decrease of $b'$ increases autoreceptors and postsynaptic receptors. It is also known that major depressive patients often show increased amounts of serotonin autoreceptors and decreased amounts of serotonin. By the consistency with these studies, we think higher amounts of autoreceptors would correspond to major depression. The series of the above mentioned phenomena is difficult to explain by the first model, but the first model is superior in terms of its deductive derivability. It is also notable that the first model predicts destabilization by the deficits of serotonin synthesis.

We suggest some experimental ideas for further verification of the validity of these models. Critical evidence would be directly given by a simple experiment. By the measurement of the dose-response curve between $k_a^{-1}[R_A]$ versus $[S]$, we can check which of the first model (eqn (12)) and the second model (eqn (13)) can explain the experimental results. It would be relatively-easy to control the dissociation constant $k_a^{-1}$ by drug injection rather than controlling the amount of receptor expression $[R_A]$. We can also check the validity of the models by using the unique characteristics of the second model. As already noted, the second model shows a pitchfork bifurcation. It is known that additive noise (fluctuation) on deterministic differential equations causes new phenomena. For example, it would be appropriate to consider the fluctuation on the amount of receptor expression. In the case of our models, it corresponds to adding a noise term onto eqn (7)–(9). With these additive fluctuations, it is known that the variance of the fluctuation expands at the critical point of the bifurcation. Thus, we will observe a great fluctuation in the amount of receptor expression or the output of the serotonergic system $f([S]_R)$ by adjusting biological entities corresponding to the bifurcation parameters. This expanding fluctuation is known as enhancement of fluctuations. Because of its non-linearity, we also predict the serotonergic system would show other characteristics known as critical slowdown and critical fluctuations. However, even if a second model explains some characteristics of the symptoms, an ethopharmacological approach is not enough to test these predictive phenomena at this time. These days, there are a lot of hypotheses to explain the mechanisms of major depression. It is necessary to analyse the structural stability of these hypotheses in the future. We expect our models will be tested by further experiments.

5 Conclusions

In conclusion, we proposed two phenomenological models about the serotonergic system. After analysing these models, we indicated the existence of an explosively increasing mechanism on the amount of autoreceptor expression at the cell membrane in the first model. We also indicated the existence of bifurcating mechanisms on the amount of autoreceptor expression at the cell membrane in the second model. We showed the consistency of the second model by interpreting our results in light of past research on major depression. Lastly, we suggested some experimental ideas for further verification of the validity of our two models. We hope further tests and analyses on our model will help our better understanding of the serotonergic system and major depression in the future.

References