Can persistent Epstein-Barr virus infection induce Chronic Fatigue Syndrome as a Pavlov feature of the immune response?

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Abstract

Chronic Fatigue Syndrome is a protracted illness condition (lasting even years) appearing with strong flu symptoms and with complex, systemic, defaiances by the immune system.

Here we study the most widely accepted picture for its genesis, namely a persistent acute mononucleosis infection, by means of non-equilibrium statistical mechanics techniques and we show how this may drive the immune system toward an out-of-equilibrium metastable state (with long life-time) displaying chronic activation of both humoral and cellular responses: a scenario with full inflammation without a direct "causes-effect" reason.

By exploiting a bridge with the neuronal scenario, we mirror killer lymphocytes T_K and B-cells to neurons and helper lymphocytes T_{H_1}, T_{H_2} to synapses, hence showing that -under minimal physical assumptions- the immune system may experience the Pavlov conditional reflex phenomenon such that if the exposition to a stimulus (EBV antigens) is too long, strong internal correlations among B, T_K, T_H may develop ultimately resulting in a persistent activation even though the stimulus itself is removed: Interestingly we found in literature several experimental findings which corroborate our outcomes.

1 Introduction

The Chronic Fatigue Syndrome (CFS) refers to a clinical condition characterized by a persistent debilitating fatigue, neurological problems and a combination of flu-like symptoms (e.g. headache, tender lymph nodes), ranging from at least 6 months up to several years [1, 2, 3, 4, 5, 6].
The estimated worldwide prevalence of CFS is $0.4\% - 1\%$ (meaning over 800000 people in the United States and approximately 240000 in the UK) with a striking socio-economical impact: The average annual total value of lost productivity in the United States is $9.1 billion [7]. Such numbers propel a continued research to determine the cause and potential therapies for CFS, whose diagnosis is still symptom based and whose origin remains elusive.
The resemblance of the CFS to a chronic form of acute infectious mononucleosis (AIM) has provoked

investigation on whether this illness (whose etiologic agent is the Epstein-Barr virus, EBV), can prompt a chronic immune reaction in the body.
In this work we try to deepen this point: By bridging between a neural system and an adaptive immune system, we show that an associative learning phenomenon might underlie a transition from an AIM to a CFS state. Our model focuses on the mutual interaction and regulation between B and T lymphocytes: when stimulated by a viral load (e.g. EBV antigens), they get activated (AIM phase); the active phase is then supposed to relax to a quiescent state once the viral load ceases. Actually, we evidence that, during such a relaxing stage, the collective behavior of the components of the system can yield non-trivial phenomena: if the AIM phase takes a relatively long time to recover (with respect to the timescale that sets the standard immune response), which is in turn related to the success of the EBV to elude immunosurveillance, a strong correlation between the activation of B and T lymphocytes can be accomplished. As a result, when the viral load has vanished and B cells remain activate for their memory role, T cells can also maintain high concentration levels since they have "learnt" that active B cells are associated to infection[1]. Therefore, as T cells display strongly inflammatory properties, we may get a state of chronically active immune response (with CFS symptoms) despite the original infection is no longer in course.

We stress that our approach, by applying basic concepts of statistical mechanics to immunology, points out *emerging* possible mechanisms leading to the development of the CFS: Of course, we can not attain the detailed interaction mechanisms which allow the phenomenon, but we can run the statistical mechanics machinery and interpret its results in keeping with the immunobiological phenomenology found in the literature [2] : Interestingly, as we will show, for this learning process to be properly fulfilled, T cells need to bypass an helper signal from specialized lymphocytes and this has been recently evidenced experimentally.

The paper is structured as follows: In Sec.2 we provide a basic background about EBV, CFS and associative learning; these topics will be merged in Sec. 3 were we present our model. Then, in Sec. 4 we show our analysis and results. Finally, our conclusions and discussions are in Sec.5, while all the mathematics involved is reported in the appendix.

2 Minimal background

In this section we provide a basic background about the main features concerning chronic fatigue syndrome, Epstein-Barr virus and classical conditioning, then, in the following sections we will merge such concepts to get an interpretation for the emergence and establishment of the CFS.

Before proceeding, it is worth introducing the main agents of the adaptive immune system [8], which will also constitute the effective agents in our modelization.

An immune response is generally triggered by the introduction into the body of an *antigen*, which may have either exogenous or endogeneous origin (e.g. toxins, bacteria, viruses, cancerogen cells). For instance, the genes of viruses that have infected a host cell can encode several proteins working as antigens.

B lymphocytes are the agents of the humoral (i.e. mediated by secreted antibodies) immune response. B-cells can produce antibodies upon their full activation, which requires antigen recognition as well as a signal from (antigen stimulated) T_H cells. From activated B cells, specific for a given antigens, memory cells are eventually formed; these are long-life cells able to respond quickly to a following exposure to the same antigen.

T lymphocytes are the agents of cellular-mediated (i.e. not involving antibodies but directly cellular

[1] In this context there is no difference among activation trough division among plasma and memory cells [8] or trough Couthino idiotipic/anti-idiotypic internal images [9, 10]; whatever signal would work finely.

[2] In a very simplified parallel, phase transition classification in statistical mechanics aware us about the existence of abrupt macroscopic changes occurring in the system under investigation, when varying its control parameters: although the mechanisms underlying e.g. the "ice-water" transition and the precipitation in an acid-base titration are completely different, the global phenomenology - described in the proper specific set of observable - behaves in the same way and a lot of mathematics and physics can be shared in their modeling (first of all the minimum energy and maximum entropy principles).

mechanisms such as lysis) response; as in standard literature, we focus on T-helper cells (T_H) and on T-cytotoxic or killer cells (T_K) which, when in their quiescent state, are referred to as T-CD8+ and T-CD4+, respectively. Quiescent T-cells can be activated upon contact with cells which have previously interacted with the antigen: T-killer cells can interact with the so-called Class I Major Hystocompatibility Complex (MHC-I) expressed by all cells, while T-helper cells can interact with the so-called Class II Major Hystocompatibility Complex (MHC-II) expressed only by antigen presenting cells (APC, e.g. macrophages, dendritic cells, B-cells). Active T_K expresses killer functions destroying infected cells, while active T_H assists other white blood cells in immunologic processes, including maturation of B cells and activation of cytotoxic T ones.

Every immune system cell is equipped to synthesize and release a variety of small molecules, called *cytokines*, that travel to other cells (both immune and nonimmune) and up/down-regulate their growth; cytokines include interferons (IFNs) and interleukins (ILs).

2.1 Chronic Fatigue Syndrome

The literature on CFS is very broad with hundreds of analysis carried out and a rich collection of data, yet the clinical implications of such findings remain uncertain and a unifying, globally accepted, picture of its etiology and pathophysiology is still missing [2, 3, 4, 5, 6].

Current theories are looking at the possibilities of neuroendocrine dysfunction, virus geneses, environmental toxins, genetic predisposition, or a combination of these: Several researches suggest that Epstein-Barr Virus (EBV), by prompting a chronic immune reaction in the body, might cause CFS. Indeed, the phenomenology reported is consistent with the idea that the syndrome may follow the occurrence of an infection yielding a massive immune response, which, for causes not yet completely clarified, may persist for long time, although the underlying infection is no longer in course. In fact, a CFS state is usually associated to an abnormal concentration and/or functioning of B-cells, T-cells and cytokines. Another interesting and robust immunological fact found in patients with CFS is an unusually high (more than 67%) increase of activated CD8+ cytotoxic T lymphocytes with MHC-II activation markers [11, 12, 13, 14, 15].

From a symptomatology viewpoint, fatigue is a common symptom, but CFS is a multi-systemic disease including even post-exertional malaise, unrefreshing sleep, widespread muscle, joint pain, cognitive difficulties, chronic (often severe) mental and physical exhaustion, muscle weakness, hypersensitivity, orthostatic intolerance, digestive disturbances and more.

2.2 The Epstein-Bar virus

EBV is one of the most successful viruses, infecting over 90% of humans and persisting for the lifetime of the person in a non pathogenic way [16, 17]. The infection can follow different pathways, in particular, it can turn in an AIM (in up to 25% cases [18]) or it can simply introduce the virus in the host organism in a non apparent way.

The virus aims to enter B-cells and, if successful, two outcomes are possible: In the first case the EBV begins a viral replication cycle (so called "lytic phase", a common feature of most viral infections), which induces the death of the infected cell, followed by the complete release of new virus particles, which are going to infect other cells; in the second case a state of latency (latent phase) is established where the "disguised" virus multiplies and stands by inside the cell, while no extracellular phenomena are observed, in such a way that no tackling by the immune system is evidenced.

During the primary infection, the latent cycle and the lytic cycle proceed in parallel and the immune system addresses most of its resources to the lytic cycle of viral replication; the infection can be asymptomatic, have non-specific symptoms, or be so massive to result in AIM. The acute phase can last up to several months and it ceases when the lytic cycle is interrupted by the immune responses or by the virus itself, then, the infection becomes latent and the host becomes a Healthy Carrier.

The possible persistence of the acute phase, despite a potent immune response against it, indicates that the virus has evolved strategies to elude the immune system. Among the different hypothesis, one

has received particular attention [19]: the antigen BCRF1[3] can simulate the signal produced by IL-10 cytokines (which normally prompts leukocytes specialized against small-sized threatening agents, like EBV's antigens) and determine a delay in the immune response. More precisely, the signal from BCRF1 inhibits the production of real IL-10; the lack of IL-10 polarizes the cellular immune response in the activation of a different kind of leukocyte, specialized in fighting against bigger-sized pathogens.

We finally report an interesting study [20] on T-cell responses, in the cases of a relatively brief (2-3 weeks) and of a protracted (4 months) acute phase. Although expansions of antigen-specific T-cells were observed in both situations, the T-cells reactivity occurred to be broad (i.e. addressed to several, both lytic and latent, antigens) and narrowly focused (i.e. mainly addressed to a singular antigen, the Early BMLF1), respectively[4].

Summarizing, a significant presence of antigen BCRF1 can determine a delay in the immune response. As a result, the immune activity may take a long time for the clearance of the infection; during this time the concentration of T_K cells remains high and polarizes against BMLF1 antigen as if an internal self-reinforcement has occurred.

2.3 Statistical Mechanics of Pavlov effect

Classical conditioning, experimentally demonstrated by Pavlov [21], is probably the most famous form of associative learning: The typical procedure for inducing classical conditioning on a subject (e.g. a dog) involves presentation of a neutral stimulus (e.g. bell ring) along with a stimulus of some significance (e.g. food). The neutral stimulus can be any event that does not result in an overt behavioral response from the subject. If the neutral and the significant stimuli are repeatedly paired, the subject eventually associates the two stimuli and starts to produce a behavioral response (e.g. salivation) even to the neutral stimulus alone.

From a statistical mechanics point of view, classical conditioning can result from the interplay of dynamic phenomena, as early investigated in [22]. More precisely, statistical mechanics usually assumes that the states of interacting "components" are fast variables, while coupling among them evolves on by far larger time scales, in such a way that, according to adiabatic hypothesis, the whole process results in two distinct timescales; for instance, in neural scenario, learning and retrieval correspond to the fast (neural) and slow (synaptic) dynamics respectively [23]. Conversely, Pavlov phenomenon emerges when these two timescales are not so spread and a unique, coupled temporal evolution must be considered for retrieval variables and learning ones.

To fix ideas, let us introduce a basic model which shall be exploited in the following. We consider two (on/off)-neurons $\sigma_i = \pm 1$ $(i = 1, 2)$ connected by one synapse $J = \pm 1$, so that $\{\sigma_i, J\} \in \{-1, 1\}$. The characteristic time for the relaxation of the two neurons is the same and denoted as τ, while the characteristic time for the relaxation of the synapse is T, with $\tau \ll T$. The time-averaged mean values of these three components are $m_i(t)$ and $w(t)$, for which $\{m_i(t), w(t)\} \in [-1, 1]$[5]. This system shows the capacity of a dynamical learning in the following sense: consider the action of two external signals, (s_1, s_2), each applied on a different neuron (σ_1, σ_2). If the stimulation of both neurons happens for a short time t (comparable with the short timescale, i.e. $t \sim \tau$), once one signal is removed, the corresponding neuron stops its activity; conversely, if the two stimuli are presented for a sufficiently long time (i.e. $t \sim T$), due to synaptic contribution, correlations within the system develop and, if one signal is turned off, its corresponding neuron remains active: We will refer to this dynamical feature as associative learning.

Let us deepen in more technical details the emergence of such a phenomenon. At first, both signals $s_1 = 1, s_2 = 1$ are applied to the related neurons [regime $(1, 1)$], consequently, the synapse can be enforced (according to Hebb's prescription [24]), that is $w(t)$ grows in time. After a given time $t_s \in [0, T]$ one

[3]The BCRF1 antigen is a Lytic Antigen sharing 70% of the human IL-10R, which is the membrane bound receptor for IL-10, see also [17].

[4]An investigation on the link among $BCRF1$ and $BMLF1$ can be found in [25]

[5]It is worth noting that here we do not use the ergodic hypoteses, so we skip the ensemble average and evaluate averages directly over time; of course, such averages must be taken over a time range at least order of τ to be meaninfull, allowing in this way the fast relaxation mode to operate.

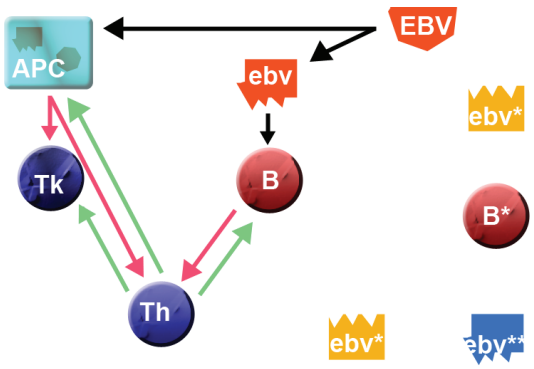

Figure 1: Circlet represent lymphocytes (T-cells in blue, B-cells in red); the red hexagon represent the Epstein-Barr Virus; irregular shapes are antigens (red) antibodies ebv* (yellow), or anti-anti-body ebv** (azure); the rectangular shape represent APCs or infected cells (healthy B-cells are not included). Different stages of the process are depicted in different colors: Infection (black arrows), Presentation (pink arrow), Activation (green arrow).

signal, say s_2, is removed [regime $(1,0)$]: if an associative learning is accomplished, we expect that under the action of s_1 alone, the system is still able to stimulate even σ_2. As we are going to show, these words can be translated into a system of stochastic differential equations describing the evolution of the neural configuration. Here we display only the evolution of averages m_1, m_2, w (details of its derivation, together with the evolution of the related correlations, are reported in the appendix):

$$\begin{cases} m_1 = \tanh\left[\beta(w m_2 + s_1)\right], \\ w = \tanh\left(\beta m_1 m_2\right), \\ m_2 = \tanh\left[\beta(w m_1 + s_2)\right]. \end{cases} \tag{1}$$

The randomness in the stochastic evolution is ruled by the term $\beta \in \mathbb{R}_0^+$, which encodes the level of noise in the system such that for $\beta = 0$ the dynamics is completely random (coherently the observable averages to zero as they are symmetrically distributed), while for $\beta \to \infty$ the hyperbolic tangent becomes the sign function and the dynamics is completely deterministic.

Finally, we stress that the statistical mechanics model we have elaborated allows a formal picture of phenomena which, actually, go far beyond Pavlov's conditional reflex; more generally, it describes processes of associative learning which has been evidenced in different biological contexts [26].

3 Our model

Recalling the evidence of two time-scales characterizing the evolution of EBV primary infection (see [20] and Sec. 2.2), as well as the statistical mechanics model introduced in Sec. 2.3, we want to exploit the concept of associative learning as a bridge between the neuronal and the immune contexts; the occurrence of such a learning process might be interpreted as a cause for the establishment of a CFS (see Sec. 2.1).

Let us sketch the evolution of the phenomenology of the EBV pathology in separate main phases where we also anticipate the mapping between the antigenic load felt by T_K and B cells respectively and the state of the two stimuli (s_1, s_2):

- *Infection and presentation*, [Regime $(0,0)$]. The virus starts the Lytic Cycle and infects permissive cells, producing antigens. The infected cells (via MHC-I) and the APCs (via MHC-II) present the processed antigen for specific T lymphocyte's recognition. A resting CD4+ T-cell must be

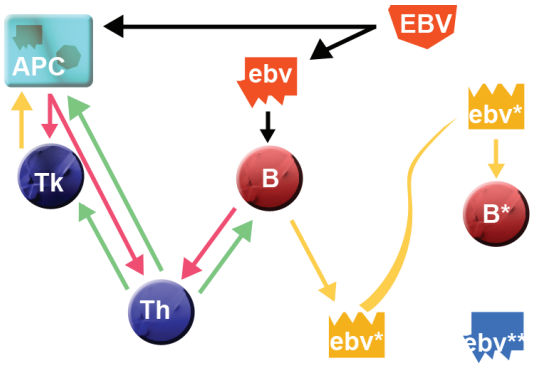

Figure 2: Kill and Memorise (yellow arrows). Agents are the same as in Fig. 1

triggered via MHC-II present on either an APC or a (antige-specific) B-cell (pink arrows in Figure 1) to become an activated T_H.

- *Activation and response*, [Regime $(1,1)$]. After having recognized the antigen, B-cells are fully activated by T_H (green arrow in Fig. 1) so that they can now start to differentiate into memory cells and plasma cells producing antibodies; T_H cells also provide the second signal, indirectly via APC, for a resting CD8+ T-cell. A resting CD8+ T-cell must be triggered by an APC via MHC-I (first signal, pink arrow in Fig. 1) and by T_H (second signal, green arrow in Fig. 1) in order to becomes a T_K.
  The activated T_K can now operate directly (yellow arrow in Fig. 2) on APC that is still in contact with the T_H, or that has been previously instructed. Meanwhile, the B-cell starts to produce antibodies (ebv*); such antibodies, being actually new antigens for the immune system, undergo to an equivalent recognition process (yellow pattern in Fig. 2), so that they stimulate their specific B*-cells for T-cell presentation [6].

- *Possible Learning*, [Regime $(1,0)$]. The immune response eventually annihilates the antigenic load, the viral load ceases and T_K cells, no longer stimulated, can undergo apoptosis pathways. As for B cells, they maintain a certain degree of stimulation (memory) even though of different nature with respect the original one. In fact, after activation, B* cells secrete antibodies (ebv**) that, being "complementary of the complementary" [27], resemble the original virus (ebv); as a result, they may act as signals themselves, that is, the antibodies ebv** sustain the stimulation of B cells [7].
  Now, according to the duration of the co-stimulation [Regime $(1,1)$] two alternative situations might happen:

  – *Healthy Carrier State, HCS.* If the Lytic Cycle has been interrupted within a relatively short time t_s by the immune response, no associative learning between the production of T_K cells and the production of B-cells is accomplished. The immune system has stored memory of the infection via memory cells and the EBV latency has established. The patient becomes a Healthy Carrier displaying specific memory healthy cells for those given antigens, as well as

[6] This standard mechanism of anti-antibodies production is due to the fact that the antibodies produced constitute a large concentration of proteins seen as anomalous by the host itself. We stress that, for this mechanism to hold, we do not need the Jerne idiotypic cascade, but only the Coutinho internal image, which has been largely revealed experimentally [9, 10].

[7] A more simplified description would require only the presence of B-memory cells for providing signalling to T_H, skipping any discussion on memory generation in B-cell network [27].

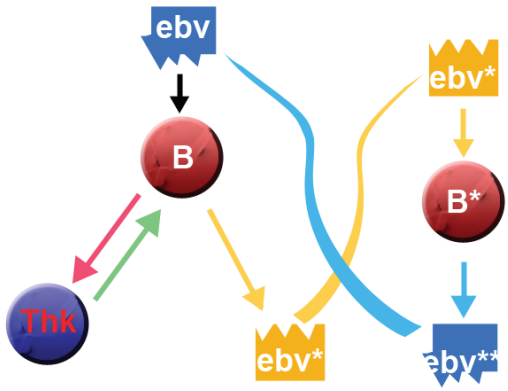

Figure 3: Learning. Agents are the same as in Fig. 1

infected resting B cells in the Latent Cycle.

– *Chronic Fatigue Syndrome, CFS.* The prolonged exposition to the (original) viral load (experimentally found to occur in the presence of large concentration of BRCF1 antigen) can lead to an associative learning between T_K and B cells production. In fact, although T_K are no longer directly stimulated by the antigen, the active state of B cells can work itself as a surrogate stimulus. Namely, T_K bypass the T_H signal and interact directly with the MHC-II signal provided by B-cells as APC. This is consistent with [20], where it is reported that the BMLF1-specific CD8+ T-cell (which should only recognize the class MHC-I) gets active bypassing the necessary T-CD4+ indirect signal. This scenario would lead to a chronic activation state and it will be further discussed in the next Section[8].

To summarize, this is our proposal for the CFS etiology: a massive presence of BMLF1 antigens makes the clearance of the infection slow so that a long co-stimulation of BMLF1-specific B and T_K cells takes place. During this stage a learning process occurs leading T_K cells to be able to detect the signal directly from B cells, hence by-passing the direct stimulation from the antigen as well as from T_H. One can think at this situation as if T_K assumed both killer and helper functions, that is as if it switched to a hybrid state.

In order to corroborate our theory, we studied the dynamical properties of our model trough analytical arguments and numerical simulations.

3.1 Formalization

In our interpretation, the viral load represents the external signal; when $s_i = +\infty$[9], the viral load is much bigger than threshold levels implied by low-dose tolerance [28], conversely, when $s_i = 0$, it is much lower. T_K and B clones specific for EBV antigen play as the neurons σ_1 and σ_2; the synapse J represents the T_H clone. Indeed, the T_H can influence both T_K and B lymphocytes, via the sub-populations T_{H_1} and T_{H_2}, respectively. Hence, the "synapsis" should be thought of as a proper combination of T_{H_1} and T_{H_2}, which results in a long relaxation time T (see Sec. 3.2).

[8] As already empathized, it is worth noting that in our model there are no suggestions for this MHC-I/MHC-II switch, as these details of the interaction are not even introduced: instead, are the results obtained ruling our stochastic dynamics -i.e. an unbalanced K/H load- that can be explainable trough this mechanism. In this sense statistical mechanics can help in understanding theoretical immunology, by conferring to thermodynamics a key role as a guide in the experimental findings.

[9] The choice of this limit value is for simplifying calculations, the physics behind is essentially the same of every "high enough" load. We stress however that the value of the field, as introduced into our stochastic system, is not coupled to the noise, such that a high value implicitly accounts for low noise (i.e. high β)

Following [28, 29, 30], the real size of the clone can be related to the time-average value of the representative spin, bounded in $[-1, 1]$, by means of an exponential law:

$$M_i = \exp\left[s_i\left(\frac{m_i(t)+1}{2}\right)\right], \tag{2}$$

where $i = 1, 2$, and

$$W = \exp\left[s_0\left(\frac{w(t)+1}{2}\right)\right], \tag{3}$$

being s_i, $i = 0, 1, 2$ a parameter that introduces the size of the pertaining population. Here we reasonably assume that the clones considered have the same size $S = 2 \times 10^{11}$, so that $s_i = \log(S)$ [8].
Now, the AIM phase corresponds to a Regime $(1, 1)$, where both T_K and B clones are stimulated by EBV antigens.
The AIM phase is estimated to last from two weeks up to two months, so we choose τ in the interval $\tau \in [14; 60]$ days.
Once the viral shedding has been interrupted by the immune responses, the T_K clone is no longer stimulated, while the B-cell clone is still managing the memory of the infection (directly or trough its conjugate specific antigen): This corresponds to the Regime $(0, 1)$.
The two-steps evolution described here is a useful schematization for the analytical approach developed in the Appendix for the special cases $\beta = 0$ and $\beta \to \infty$. More generally, the system of coupled differential equations Eqs. (1) can be solved numerically for any value of β and in the presence of continuous signals. In particular, while s_2 is still non-null over the whole range considered, s_1 can be chosen as exponentially decaying (being t_s characteristic time for vanishing), in agreement with experimental findings [8].
Despite the system is well described by the stochastic dynamical equations (Eqs. (1)), we can improve the picture by including proper terms accounting for the collective behavior due to interaction with other lymphocytes and immune agents, that is, we mimic both quiescence induction and internal signaling to apoptosis by introducing further two small negative fields $|\epsilon_1|, |\epsilon_2| \ll 1$, in such a way that the effective fields acting on the two clones are $\tilde{s}_1 = s_1 + \epsilon_1$ and $\tilde{s}_2 = s_2 + \epsilon_2$, respectively. We underline that the statistical mechanics reason for these small fields, whose effect would otherwise be negligible being them infinitesimal, is breaking the gauge symmetry of the model, so to allow a quiescent state in the absence of signals.

3.2 On the mixed synapse and timescales

In our model the synapse plays the role of the helper T-cell. Upon activation, helper T cells differentiate in two major subtypes known as T_{H_1} and T_{H_2}: Beyond other functions, the former maximizes the proliferation of cytotoxic CD8+, the latter stimulates B-cells into proliferation; also, they both produce cytokines which are aimed to their own proliferation and cross-regulate each other's development and activity [8]. The net result is that, once the T_H response begins to develop, it may get polarized in one of the two directions (either Type 1 or Type 2), due to auto-amplification and cross regulation [8].

Now, when the two subpopulations are completely balanced and small (corresponding to a quiescent state) none of the two prevails so that, in our equivalent model, there is no link between B and T_K ($w = 0$) and no learning can be established among them (as intuitively $T \to \infty$). Conversely, when one of the two prevails the synapse is onset ($w \neq 0$), so that B and T_K can (indirectly) interact (still retaining a large timescale T compared to the single clone one τ).
Hence, as envisaged by the scheme in Fig. 4 the central spin, playing the role of the synapse, can be thought of as a combination of two sub-populations. An effective way to relate the states of T_{H_1} and T_{H_2} with the overall state of T_H is given by the following "average", where we denote with w_1 and w_2 the "magnetizations" corresponding to the two sub-populations:

$$w = \frac{w_1 w_2}{4}[w_1 + w_2 + |w_1| + |w_2| + |w_1 - w_2|]. \tag{4}$$

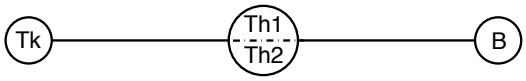

Figure 4: Schematic representation of the three-spins system considered, where the complex structure of the synapse (central spin) is explicitly envisaged.

Indeed, this combination is in agreement with the immunological phenomenology and consistent with the model we are introducing: balanced, quiescent sub-populations correspond to $w = 0$, a large unbalance in favor of any of the two sub-population means $w < 0$, while when they are both stimulated we have a reinforcement effect ($w > 0$).

In general, one can assume that the characteristic timescales of lymphocyte growth are the same, independently of the particular type, that is, T_H, T_K and B cells require the same time τ to adjust their concentrations responding to a signal. Anyhow, in our model, the three agents considered feature different degrees of complexity: while σ_1 and σ_2 can be thought of as homogenous populations, the synapse J displays inner degrees of freedom, being the combination of the two sub-populations T_{H_1} and T_{H_2}. Consequently, we expect that its relaxation time T is larger than τ. In other words, the typical time necessary for the sub-populations to adjust is much longer than τ.

The characteristic time for the response of B and T_K is taken to be $\tau \in [14, 60]$, since the AIM phase is estimated to range from two weeks up to two months, while for our synapse we reasonably choose $T = 90$ days because the average duration of the AIM phase, prequel to the CFS, is estimated to be from three months up to seven. However, in our model the tunable parameter is the ratio τ/T, so the previous choice does not modify the results. Furthermore, while the signal s_2 is constant, the signal s_1 (representing the real antigenic load) is taken exponentially decaying, in such a way that the effective time of its offset is t_s; similarly, in the analytical approach in the appendix the signal is active for a time $t \in [0, t_s]$, while the second regime holds for $t \in [t_s, \infty)$, with $\tau < t_s < T$: In any case we find that the value of t_s crucially determines the final equilibrium state.

3.3 The role of the latent and lytic cycles

In this section we want to deepen a way (tipycal of all herpesviruses) which may further contribute to lengthen the hospitalization time of a CFS patient. In fact EBV, once the infection has been established in the host body, may hide away from immune recognition and opportunely switch among cycles of latency and cycles of lytic replication, somehow mirroring a switch among a quiescent and an active external stimulus acting on the immune system. In fact, during latency, EBV mainly manages minimal tasks as inhibiting apoptosis and blocking viral lytic replication, while, during the lytic phase, EBV syntetizes proteins from many more viral genes, allowing for nucleotide biosynthesis, RNA processing, viral DNA replication, etc.

As a consequence, within the framework based on "Pavlov phenomenology" we are using to explain the transition from an AIM to a CFS scenario, these re-activations display significantly different outcomes in healthy carriers and in CFS patients. In fact, as shown in Fig. 5, for the formers, whose infection walked off quickly (toward an healthy carrier final state), sequential impulsive stimuli do not have particular consequences, while, for the latters, whose infection has been prolonged enough to allow the correlation via the Helpers, basically each time there is an impulsive reactivation, this thwarts the natural de-learning.

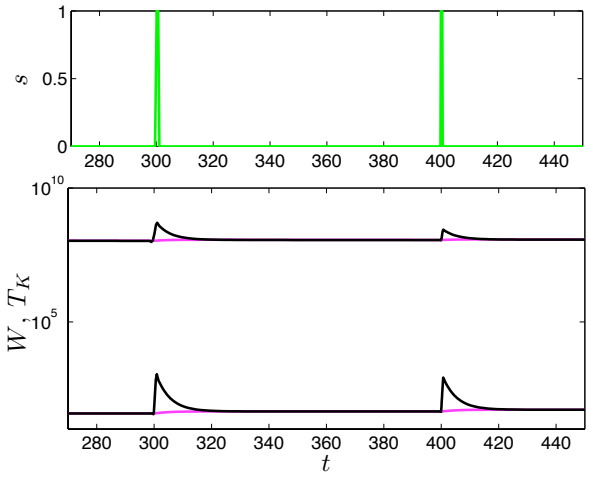

Figure 5: Upper panel: impulsive stimulus $s = s1_1 = s_2$ as a function of time; Lower panel: immune response in terms of concentration of T_K (dark line) and of T_H (bright line) for an healthy carrier (smaller values) and a CFS patient (higher values).

4 Results

The stochastic system of Eqs. (1) is solved numerically by means of standard Runge-Kutta packages for Matlab.
For the sake of clearness, a fully rigorous solution of the system is shown in the appendix, nonetheless, here it is worth introducing the whole set of observables we need to consider. Namely we have to deal with averages and correlations:

$$w = \langle J \rangle_\tau,\ m_1 = \langle \sigma_1 \rangle_\tau,\ m_2 = \langle \sigma_2 \rangle_\tau, m_{12} = \langle \sigma_1 \sigma_2 \rangle_\tau,$$

$$m_{01} = \langle J\sigma_1 \rangle_\tau,\ m_{02} = \langle J\sigma_2 \rangle_\tau,\ m_{012} = \langle J\sigma_1\sigma_2 \rangle_\tau,$$

where the average $\langle \cdot \rangle_\tau$ is meant over the time as explained in Sec. 2.3. We set our initial conditions $\mathbf{m}(0)$ using concentrations expressed in cells/μL and keeping in mind that, in a healthy body, a given clone has an incidence of 1 over 10^5 cells with respect to the whole population; by using the normal values for lymphocytes concentrations and the relative translation in terms of magnetizations (see Eq. 2) reported in Tab. 1, we get:

$$\mathbf{m}(0) = \begin{cases} w(0) \sim 0 \\ m_1(0) = -0.971 \\ m_2(0) = -0.938 \\ m_{12}(0) = m_1(0) \cdot m_2(0) \\ m_{01}(0) = 0 \\ m_{02}(0) = 0 \\ m_{012}(0) = 0 \end{cases} \tag{5}$$

Notice that the initial value for the correlation m_{12} as the product of the two concentrations m_1, m_2 is a useful condition to initialize the evolution (implicitly assuming uncorrelation), and we will use it during numerical integration.

In order to recover the two cases of HSC patient and CFS patient, as reported in Sec. 2.2, we consider two different situations, corresponding to a short ($t_s = 5$ days) and to a long ($t_s = 100$ days) AIM phase, respectively. The other parameters holding for both patients are:

$$\tau = 30,\ T = 90,$$

Table 1: Data for initial conditions [8]. Notice that we do not specify the relative concentrations of T_{H_1} and T_{H_2}, whose supposed equality at rest imposes $w \sim 0$, but only of their sum T_H.

Agent	Concentration (cells/μL)	%	$M_i(0)$ (specific cells/μL)	$m_i(0)$ (adimens.)
T_H	1000.50	46	0.010	-0.815
T_K	413.25	19	0.004	-0.971
B	500.25	23	0.005	-0.938

$$s_1 = 1000,\ s_2 = \exp^{-(t-t_s)/80},$$

$$\epsilon_1 = -1.0,\ \epsilon_2 = -1.0.$$

We also fix the level of noise as low ($\beta = 6.5$), while later we will discuss the case of high noise.

Patient 1: HSC Scenario.
As shown in Fig. 6, during the AIM phase ($t < t_s = 5$ days), both signals s_1 and s_2 are active and, as responses, m_1, m_2 grow up, meaning that T_K and B clones are proliferating; the synapse also increases as both its afferent inputs are growing (correlations begin).
As the real viral load is diminishing, T_K concentration decreases and finally reaches a value comparable with the initial one. Conversely, B clones, being still stimulated, maintain high levels of concentration. In Fig. 8 we focus on the behavior of T_H and T_K, showing their evolution directly in terms of their concentrations: the latter reach a maximum ($\sim 10^3$ cells/μL) at very short times and then relax to approximately 10^2 cells/μL.

Patient 2: CFS Scenario.
As shown in Fig. 7, during the AIM phase ($t < t_s = 100$ days), the concentrations of B, T_K and T_H increase as a result of a viral load ($s_1, s_2 > 0$). This time, the signal on T_K lasts long enough for T_K and T_H to reach high levels (both $\sim 10^5$ cells/μL) and, even when the signal is switched off their concentrations are much larger than the one pertaining to Patient 1.

The outcomes for the two cases are compared in Fig. 8 directly in terms of concentrations.

Finally, when the level of noise is high, we expect that the effects due to interaction get more and more negligible. Indeed, in this model "low" and "high" level of noise are not referred to a specific "critical value", as this model does not break ergodicity by itself; conversely, since the noise level is coupled to the averaged energy in the system $E = \langle J\sigma_1\sigma_2 \rangle$, the product among them, i.e. either $\beta E > 1$, or $\beta E < 1$, defines the levels. For instance, the case $\beta = 0.8$ is shown in Fig. 9: notice that independently of the duration of s_1, both the averages m_1 and m_2 relax to small values.

To summarize, according to the duration of the AIM phase, which is in turn related to the success of the EBV strategy (Sec. 2.2), we can get two possible scenarios. If the AIM phase is rather fast, when the viral load has vanished, B cells are continuously activated, while the concentration of T_K cells recovers normal values hence we reach an equilibrium state corresponding to an healthy carrier state.
Conversely, if the AIM phase is prolonged, a strong correlation between the active B and T_K lymphocytes can be accomplished; as a result, when the viral load has vanished, again B are continuously activated but T_K lymphocytes can maintain high levels concentrations. This is the actualization of a conditional reflex and, from a mathematically point of view it arises from the large correlation w stored, able to sustain the active status of T_K.

5 Conclusion and Discussion

The Chronic Fatigue Syndrome (CFS) has been studied for almost thirty years in the whole biological, medical and psychological world, being identified with tens of medical terms; as well, a full consensus on its genesis, physiopathology and treatment has not been reached yet.

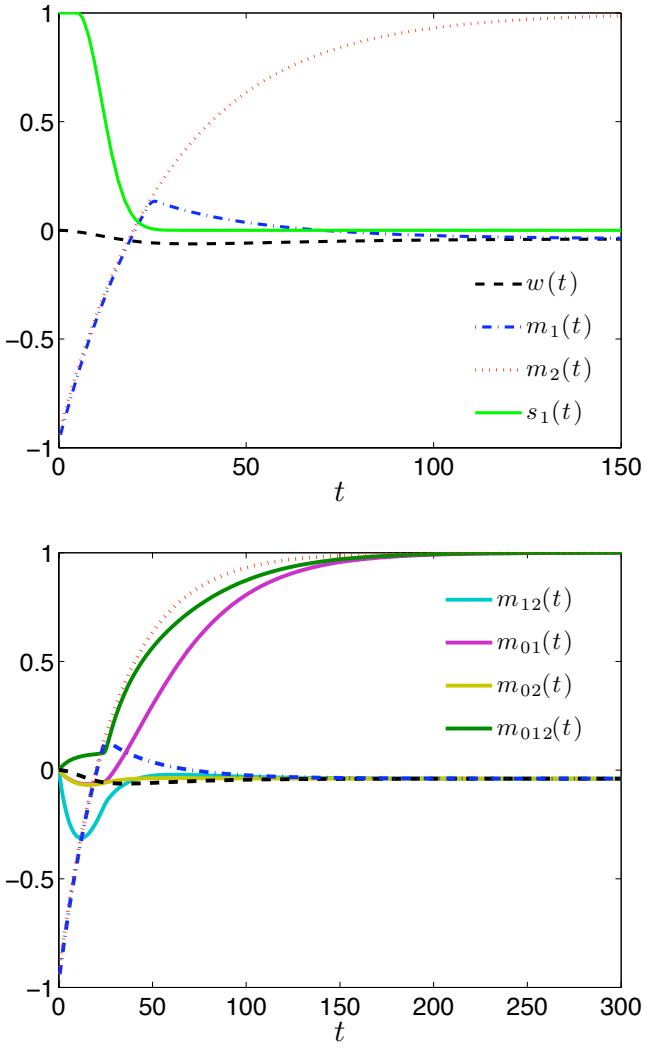

Figure 6: (Color on line) Top panel: Averages w, m_1 m_2 and signal s_1 as a function of time (zoom on the early regime). Bottom panel: the same averages ad their correlations as a function of time, as shown in the legends; time is measured in days. The signal on Tk vanishes at around time $t_s = 5$. The level of noise is low and fixed at $\beta = 6.5$.

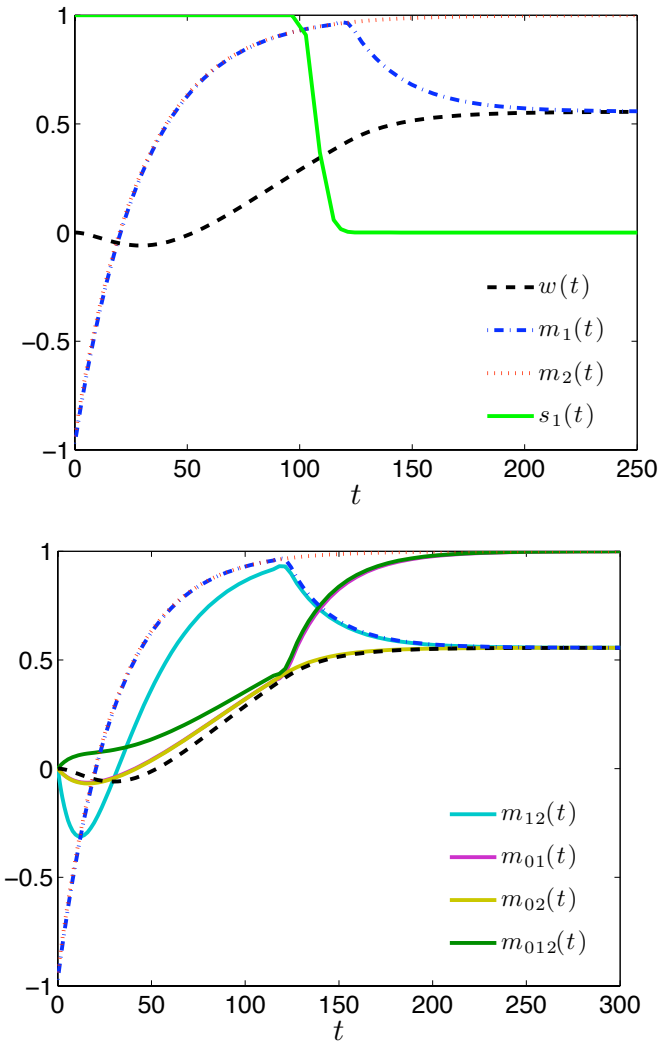

Figure 7: (Color on line) (Color on line) Top panel: Averages w, m_1 m_2 and signal s_1 as a function of time (zoom on the early regime). Bottom panel: the same averages ad their correlations as a function of time, as shown in the legends; time is measured in days. The signal on Tk vanishes at around time $t_s = 100$. The level of noise is low and fixed at $\beta = 6.5$.

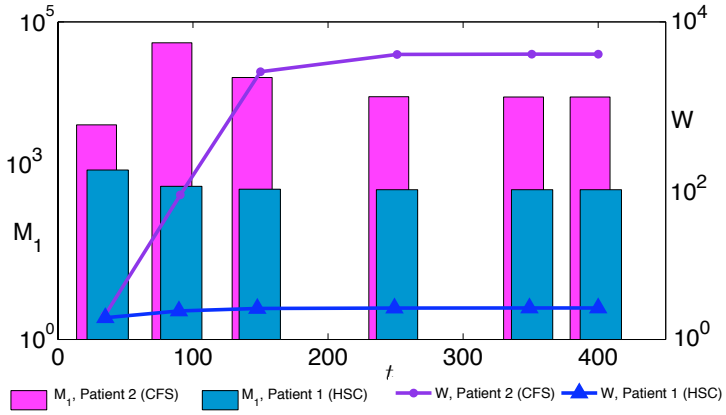

Figure 8: (Color on line) Concentrations of T_K cells (histogram, left vertical axis) and of T_H cells (curves, right vertical axis) for the two patients considered in the case of small noise.

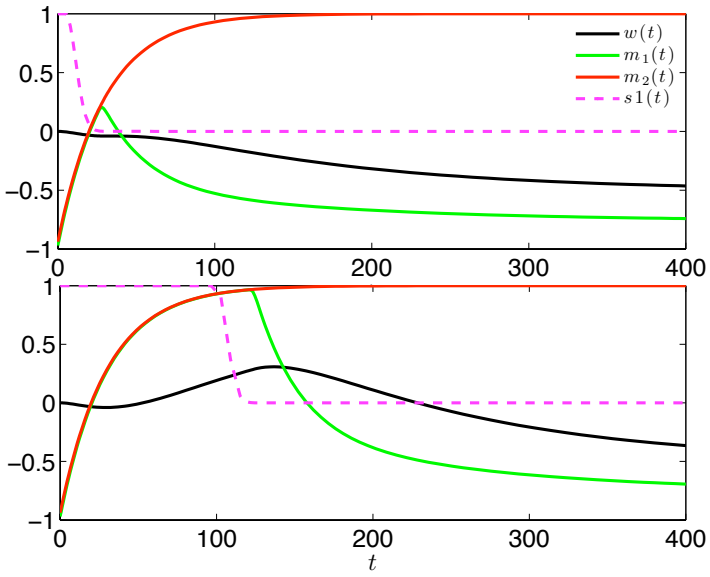

Figure 9: (Color on line) Averages w, m_1 m_2 and signal s_1 (dashed line) as a function of time for Patient 1 (top panel) and Patient 2 (bottom panel). The level of noise is low and fixed at $\beta = 0.8$.

It is just the lack of a clear-cut picture that makes theoretical models very useful tools in order to get information about the possible causes of this disease. The present work aims to take advantage of the statistical mechanics lenses to investigate why and how the CFS may establish. Of course, the model cannot simulate the whole immune system, which is much too complicated, rather, it has to get a compromise between simplification and inclusion of most important characters, the latter chosen according to experimental facts.

Our explanation is inspired by the well-known conditional reflex phenomenon in neurobiology, which, from a statistical mechanics perspective, can be recovered in terms of thermodynamic relaxation of complex systems [22]. Given two agents (e.g. two neurons or B and T_K lymphocytes) and a coupling (e.g. the synapse or the T_H lymphocytes) joining them, provided that two agents are contemporary stimulated by two related signals (e.g. neural stimuli or antigens), then even though one of the signal is switched off the two agents remain both active; this realizes the so-called "associative learning".
More precisely, we find that, if the Epstein-Barr virus infection is prolonged in time, T_K and B cells can reach high values of concentration, moreover, the latter have time enough to produce the image ebv**. As a result, when the (real) viral load has vanished, B cells are still stimulated, while T_K may maintain high concentration levels since they have learnt the correlation between presence-of-antigen and B-activation. Interestingly, this learning process also implies that T_K can get activated by-passing the signal from T_H cells and this has been recently found experimentally.
Therefore, our model and our analysis suggest that the CFS, meant as a chronically active immune state, can arise from an associative-learning phenomenon. Such a suggestion may be exploited in future experiments in order to shed light on the etiology of this syndrome; furthermore, at least at a theoretical physics level, unlearning processes are actually possible.

Finally, it is worth stressing the "guide role" of statistical mechanics when modeling biological systems: in fact this approach, constraining the system to respect thermodynamics, can provide a working picture possibly inspiring experimental path to be walked. In this sense, relying on natural and minimal assumptions, we evidence the emergence of a subtle role by T_K (able to bypass a standard double signal activation provided by antigen plus helpers), and, indeed, we found its consistency with experimental data. In fact in [31], it has been documented that a CD8+ T receptors that normally recognize MHC-I signals can exhibit dual specificity recognizing also an antigen in the context of the MHC-II.

6 Appendix: Evolution toward steady states of the system

The system whose dynamics is investigated trough the paper can be resumed as follows:
$\sigma_{i=1} = \sigma_1$, $\sigma_{i=2} = \sigma_2$ are the effectors (as neurons in the neurobiology counterpart), while J_{12} is the synapse; further we name s_1, s_2 the external fields acting respectively on σ_1, σ_2.
Each of the variable experiences the same structure of (external/internal) fields, namely (calling $\sigma_{i=3} = J_{12}$ to preserve the symmetry)

$$\langle \sigma_i \rangle = \langle \tanh \Big(\beta \sigma_{i+1} \sigma_{i+2} + s_i \Big) \rangle = a_i + b_i \langle \sigma_{i+1} \sigma_{i+2} \rangle, \tag{6}$$

where

$$a_i = \frac{1}{2} \left[\tanh(\beta + s_i) + \tanh(-\beta + s_i) \right], \tag{7}$$

$$b_i = \frac{1}{2} \left[\tanh(\beta + s_i) - \tanh(-\beta + s_i) \right]. \tag{8}$$

Overall we have the following system

$$\langle \sigma_1 \rangle = \langle \tanh(\beta J \sigma_2 + s_1) \rangle, \tag{9}$$

$$\langle J \rangle = \langle \tanh(\beta \sigma_1 \sigma_2) \rangle = \langle \sigma_1 \sigma_2 \rangle \tanh(\beta), \tag{10}$$

$$\langle \sigma_2 \rangle = \langle \tanh(\beta J \sigma_1 + s_2) \rangle. \tag{11}$$

The time scale of J is $T \ll \tau$, τ being the time scale of the σ and we pose $\frac{1}{T}+\frac{1}{\tau}=\frac{1}{\tau'}$, $\frac{2}{\tau}+\frac{1}{T}=\frac{1}{\tau''}$.

The averages evolve accordingly to

$$\begin{aligned}
\tau\frac{d\langle\sigma_1\rangle}{dt} &= -\langle\sigma_1\rangle + a_1 + b_1\langle J\sigma_2\rangle, && (12)\\
T\frac{d\langle J\rangle}{dt} &= -\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle, && (13)\\
\tau\frac{d\langle\sigma_2\rangle}{dt} &= -\langle\sigma_2\rangle + a_2 + b_2\langle J\sigma_1\rangle, && (14)
\end{aligned}$$

while the correlations evolve accordingly to

$$\begin{aligned}
\frac{d\langle\sigma_1\sigma_2\rangle}{dt} &= \frac{-2}{\tau}\langle\sigma_1\sigma_2\rangle + \frac{1}{T}\Big(a_1\langle\sigma_2\rangle + b_1\langle J\rangle + a_2\langle\sigma_1\rangle + b_2\langle J\rangle\Big), && (15)\\
\frac{d\langle J\sigma_1\rangle}{dt} &= \frac{-1}{\tau'}\langle J\sigma_1\rangle + \frac{1}{T}\tanh(\beta)\langle\sigma_2\rangle + \frac{1}{\tau}\Big(a_1\langle J\rangle + b_1\langle\sigma_2\rangle\Big), && (16)\\
\frac{d\langle J\sigma_2\rangle}{dt} &= \frac{-1}{\tau'}\langle J\sigma_2\rangle + \frac{1}{T}\tanh(\beta)\langle\sigma_1\rangle + \frac{1}{\tau}\Big(a_2\langle J\rangle + b_2\langle\sigma_1\rangle\Big), && (17)\\
\frac{d\langle J\sigma_1\sigma_2\rangle}{dt} &= \frac{-2}{\tau''}\langle J\sigma_1\sigma_2\rangle + \frac{1}{T}\tanh(\beta) + \frac{1}{\tau}\Big(a_1\langle J\sigma_2\rangle + b_1 + a_2\langle J\sigma_1\rangle + b_2\Big). && (18)
\end{aligned}$$

The source of $\langle\sigma_1\rangle$ is s_1 as well as s_2 does for $\langle\sigma_2\rangle$, while the source for $\langle J\rangle$ is the internal correlation $\langle\sigma_1\sigma_2\rangle$.

Such a system experiences four different regimes [zero signal, one signal (left), one signal (right), both signals], whose dynamics we are going to analyze.

6.1 Regime $s_1 = 0, s_2 = 0$: No signalling.

Glauber dynamics reduces to

$$\begin{aligned}
T\frac{d\langle J\rangle}{dt} &= -\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle, && (19)\\
\tau\frac{d\langle\sigma_1\rangle}{dt} &= -\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle, && (20)\\
\tau\frac{d\langle\sigma_2\rangle}{dt} &= -\langle\sigma_2\rangle + \tanh(\beta)\langle J\sigma_1\rangle, && (21)\\
\frac{d\sigma_1\sigma_2}{dt} &= \frac{1}{\tau}\Big(-2\langle\sigma_1\sigma_2\rangle + 2\tanh(\beta)\langle J\rangle\Big), && (22)\\
\frac{d\langle J\sigma_1\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_1\rangle + \frac{1}{\tau'}\tanh(\beta)\langle\sigma_2\rangle, && (23)\\
\frac{d\langle J\sigma_2\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_2\rangle + \frac{1}{\tau'}\tanh(\beta)\langle\sigma_1\rangle, && (24)\\
\frac{d\langle J\sigma_1\sigma_2\rangle}{dt} &= -\frac{1}{\tau''}\langle J\sigma_1\sigma_2\rangle + \frac{1}{\tau''}\tanh(\beta). && (25)
\end{aligned}$$

As it is immediate to see, the global dynamics spreads over four different independent subdynamics, namely $\langle\sigma_1\rangle \Longleftrightarrow \langle J\sigma_2\rangle$, $\langle\sigma_2\rangle \Longleftrightarrow \langle J\sigma_1\rangle$, $\langle\sigma_1\sigma_2\rangle \Longleftrightarrow \langle J\rangle$, $\langle J\sigma_1\sigma_2\rangle$, whose asymptotic regime is given by $\langle J\rangle = \langle\sigma_1\sigma_2\rangle = 0$, $\langle\sigma_1\rangle = \langle J\sigma_2\rangle = 0$, $\langle\sigma_2\rangle = \langle J\sigma_1\rangle = 0$, $\langle J\sigma_1\sigma_2\rangle = \tanh(\beta)$.

The general solution of the problem can be obtained coupling the four different subdynamics.

By the first set we get

$$\begin{aligned}
\frac{d\langle J\rangle}{dt} &= -\frac{1}{T}\langle J\rangle + \frac{\tanh(\beta)}{T}\langle\sigma_1\sigma_2\rangle && (26)\\
\frac{d\langle\sigma_1\sigma_2\rangle}{dt} &= -\frac{2}{\tau}\langle\sigma_1\sigma_2\rangle + \frac{2\tanh(\beta)}{\tau}\langle J\rangle. && (27)
\end{aligned}$$

whose matrix can be written as

$$\begin{pmatrix} 1/T & -\tanh(\beta)/T \\ -2\tanh(\beta)/T & 2/T \end{pmatrix}.$$

We can diagonalize the subdynamics by looking for solutions as linear combinations as

$$Y(t) = a\langle J(t)\rangle + b\langle \sigma_1(t)\sigma_2(t)\rangle, \tag{28}$$

and we can associate to this new variable a caracteristic timescale $\bar{\tau}$ as

$$\begin{aligned} \bar{\tau}\frac{dY}{dt} = -Y \Longrightarrow \frac{a\bar{\tau}}{T}\Big(-\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle\Big) \qquad (29)\\ + \quad \frac{2b\bar{\tau}}{\tau}\Big(-\langle\sigma_1\sigma_2\rangle + \tanh(\beta)\langle J\rangle\Big) = -a\langle J\rangle - b\langle\sigma_1\sigma_2\rangle. \end{aligned}$$

Namely we get the system

$$\Big(1-\frac{\bar{\tau}}{T}\Big) + 2\frac{\bar{\tau}}{\tau}\tanh(\beta)b = 0 \tag{30}$$

$$\frac{\bar{\tau}}{T}\tanh(\beta)a + \Big(1-2\frac{\bar{\tau}}{T}\Big)b = 0. \tag{31}$$

Let us work out $\bar{\tau}(\beta)$:

$$\left(\frac{1}{\bar{\tau}}\right)^2 - \left(\frac{1}{\bar{\tau}}\right)\left[\frac{1}{T}\frac{2}{\tau}\right] + \frac{2}{\tau T}\frac{1}{\cosh^2(\beta)} = 0, \tag{32}$$

whose roots are

$$\frac{1}{\bar{\tau}_{1,2}\,(\beta)} = \frac{1}{2}\left[\frac{1}{T}+\frac{2}{\tau} \pm \sqrt{\left(\frac{1}{T}+\frac{2}{\tau}\right)^2 - \frac{8}{\tau T\cosh^2(\beta)}}\right]. \tag{33}$$

Now we have to solve for a, b in $Y = a\langle J\rangle + b\langle\sigma_1\sigma_2\rangle$. We can define $a = c2\frac{\bar{\tau}}{T}\tanh(\beta)$, $b = -c(1-\frac{\bar{\tau}}{T})$, by which

$$Y_0(t) = c_0\Big(2\frac{\bar{\tau}_1}{\tau}\tanh(\beta)\langle J\rangle - (1-\frac{\bar{\tau}_1}{T})\langle\sigma_1\sigma_2\rangle\Big) \tag{34}$$

$$Y_{12}(t) = c_{12}\Big(2\frac{\bar{\tau}_2}{\tau}\tanh(\beta)\langle J\rangle - (1-\frac{\bar{\tau}_2}{T})\langle\sigma_1\sigma_2\rangle\Big), \tag{35}$$

on which we can fix c_0, c_{12} as $c_0 = \tau/2\bar{\tau}_1\tanh(\beta)$, $c_{12} = -1/(1-\bar{\tau}_2/T)$. From eq.(32) we get

$$\tanh(\beta) = \sqrt{\frac{\tau T}{2}}\sqrt{\left(\frac{1}{\bar{\tau}}-\frac{1}{T}\right)\left(\frac{1}{\bar{\tau}}-\frac{2}{\tau}\right)}$$

and we can solve for Y_0, Y_{12}:

$$Y_0(t) = \langle J\rangle + \sqrt{\frac{\tau}{2T}}\sqrt{\frac{\frac{1}{T}-1\bar{\tau}_1}{\frac{2}{\tau}-\frac{1}{\bar{\tau}_1}}}\langle\sigma_1\sigma_2\rangle, \tag{36}$$

$$Y_{12}(t) = \langle\sigma_1\sigma_2\rangle - \sqrt{\frac{2T}{\tau}}\sqrt{\frac{\frac{1}{\bar{\tau}_2}-\frac{2}{\tau}}{\frac{1}{\bar{\tau}_2}-\frac{1}{T}}}\langle J\rangle, \tag{37}$$

so we get the form

$$Y_0(t) = \langle J(t)\rangle + A_0\langle\sigma_1(t)\sigma_2(t)\rangle, \tag{38}$$

$$Y_{12}(t) = \langle\sigma_1(t)\sigma_2(t)\rangle - A_{12}\langle J(t)\rangle, \tag{39}$$

with

$$A_0 = \sqrt{\frac{\tau}{2T}}\sqrt{\frac{\frac{1}{T}-1\bar{\tau}_1}{\frac{2}{\tau}-\frac{1}{\bar{\tau}_1}}}, \quad A_{12} = \sqrt{\frac{2T}{\tau}}\sqrt{\frac{\frac{1}{\bar{\tau}_2}-\frac{2}{\tau}}{\frac{1}{\bar{\tau}_2}-\frac{1}{T}}}.$$

By the eigenvalues found in eq.s(33) we can build the eigenvectors $V_1 = (V_{11}, V_{12}), V_2 = (V_{21}, V_{22})$ as

$$V_{11} = \tanh(\beta)/T,\ V_{12} = (\frac{1}{2T} - \frac{1}{\tau} - \frac{1}{2}\sqrt{\Delta}),$$

$$V_{21} = \tanh(\beta)/T,\ V_{22} = (\frac{1}{2T} - \frac{1}{\tau} + \frac{1}{2}\sqrt{\Delta}),$$

being $\Delta = (1/T + 2/\tau)^2 - \frac{8}{T\tau\cosh^2(\beta)}$, by which, finally we get

$$\langle J(t)\rangle = C_1 V_{11} e^{-\frac{t}{\bar{\tau}_1}} + C_2 V_{12} e^{-\frac{t}{\bar{\tau}_2}}, \tag{40}$$

$$\langle \sigma_1(t)\sigma_2(t)\rangle = C1 V_{21} e^{-\frac{t}{\bar{\tau}_1}} + C_2 V_{22} e^{-\frac{t}{\bar{\tau}_2}}. \tag{41}$$

By the second set we get

$$\tau\frac{d\langle\sigma_1\rangle}{dt} = -\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle, \tag{42}$$

$$\tau'\frac{d\langle J\sigma_2\rangle}{dt} = -\langle J\sigma_2\rangle + \tanh(\beta)\langle\sigma_1\rangle. \tag{43}$$

whose matrix can be written as

$$\begin{pmatrix} 1/\tau & -\tanh(\beta)/\tau \\ -\tanh(\beta)/\tau' & 1/\tau' \end{pmatrix}.$$

Again we can write a solution in the general form $Y(t) = a\langle\sigma_1\rangle + b\langle J\sigma_2\rangle$ and label $\bar{\tau}$ its characteristic timescale such that

$$\bar{\tau}\frac{dY}{dt} = -Y$$

$$\Longrightarrow \frac{\bar{\tau}}{\tau}a\Big(-\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle\Big) + \frac{\bar{\tau}}{\tau'}b\Big(-\langle J\sigma_2\rangle + \tanh(\beta)\langle\sigma_1\rangle\Big) =$$
$$= -a\langle\sigma_1\rangle + b\langle J\sigma_2\rangle,$$

and write the system

$$(1 - \frac{\bar{\tau}}{\tau})a + \frac{\bar{\tau}}{\tau'}\tanh(\beta)b = 0, \tag{44}$$

$$\frac{\bar{\tau}}{\tau}\tanh(\beta)a + (1 - \frac{\bar{\tau}}{\tau'})b = 0. \tag{45}$$

Again we can find the eigenvalues $\bar{\tau}_{1,2}^{-1}(\beta)$ as

$$\frac{1}{\bar{\tau}_{1,2}(\beta)} = \frac{1}{2}\Big(\frac{1}{\tau} + \frac{1}{\tau'} \pm \sqrt{(\frac{1}{\tau} + \frac{1}{\tau'})^2 - \frac{4}{\tau\tau'}(1 - \tanh^2(\beta))}\Big) \tag{46}$$

and write the general solution in the form

$$\langle\sigma_1(t)\rangle = \frac{C_1\tanh(\beta)}{\tau}e^{-\frac{t}{\bar{\tau}_1}} - \frac{C_2\tanh(\beta)}{\tau}e^{-\frac{t}{\bar{\tau}_2}}, \tag{47}$$

$$\langle J\sigma_2(t)\rangle = -\frac{C_1}{2}(\frac{1}{T} - \sqrt{\Delta})e^{-\frac{t}{\bar{\tau}_1}} - \frac{C_2}{2}(\frac{1}{T} - \sqrt{\Delta})e^{-\frac{t}{\bar{\tau}_2}}, \tag{48}$$

Δ being $(1/\tau + 1/\tau')^2 - (4/\tau\tau')(1 - \tanh(\beta))$.

For the two other subsystems we can proceed exactly as we did so far and verify that, even though on different timescales, all the observables (magnetizations and correlations) converge to zero.

6.2 Regime $s_1 = 0, s_2 = \infty$: One infinite signal.

Let us start with the following conditions: $s_1 = 0, s_2 = \infty$, then we have $a_1 = 0, b_1 = \tanh(\beta), a_2 = 1, b_2 = 0$ and the evolution of the system can be written as

$$\begin{aligned}
T\frac{d\langle J\rangle}{dt} &= -\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle, && (49)\\
\tau\frac{d\langle\sigma_1\rangle}{dt} &= -\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle, && (50)\\
\tau\frac{d\langle\sigma_2\rangle}{dt} &= -\langle\sigma_2\rangle + 1, && (51)\\
\tau\frac{d\langle\sigma_1\sigma_2\rangle}{dt} &= -2\langle\sigma_1\sigma_2\rangle + \tanh(\beta)\langle J\rangle + \langle\sigma_1\rangle, && (52)\\
\frac{d\langle J\sigma_1\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_1\rangle + \frac{1}{\tau'}\tanh(\beta)\langle\sigma_2\rangle, && (53)\\
\frac{d\langle J\sigma_2\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_2\rangle + \frac{1}{T}\tanh(\beta)\langle\sigma_1\rangle + \frac{1}{\tau}\langle J\rangle, && (54)\\
\frac{d\langle J\sigma_1\sigma_2\rangle}{dt} &= -\frac{1}{\tau''}\langle J\sigma_1\sigma_2\rangle + \frac{1}{\tau}\langle J\sigma_1\rangle + \frac{1}{\tau'}\tanh(\beta). && (55)
\end{aligned}$$

The presence of a signal in the second channel bridges the two sets $(\langle\sigma_1(t)\rangle, \langle J\sigma_2(t)\rangle)$ and $(\langle\sigma_1(t)\sigma_2(t)\rangle, \langle J(t)\rangle)$ such that the latter, if the system has experienced the field enough time to learn correlations, will assume high values: a signal in the second channel may induce a raise of response even in the first channel.

Let us divide the system again by considering the following natural sub-dynamics

$$\begin{aligned}
T\frac{d\langle J\rangle}{dt} &= -\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle, && (56)\\
\tau\frac{d\langle\sigma_1\sigma_2\rangle}{dt} &= -2\langle\sigma_1\sigma_2\rangle + 2\tanh(\beta)\langle J\rangle\\
&+ [\langle\sigma_1\rangle - \tanh(\beta)\langle J(t)\rangle]. && (57)
\end{aligned}$$

We observe at first that the term $[\langle\sigma_1\rangle - \tanh(\beta)\langle J(t)\rangle]$ is a novelty with respect to the same equations in the regime $s_1 = 0, s_2 = 0$ and represents the "unlearning source": if the conditional reflex (which we are going to introduce) is not reinforced, it will tend to vanish.
The source of such a conditional reflex can be found by looking at the other subsystem, namely

$$\begin{aligned}
\tau\frac{d\langle\sigma_1\rangle}{dt} &= -\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle, && (58)\\
\frac{d\langle J\sigma_2\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_2\rangle + \frac{1}{\tau'}\tanh(\beta)\langle\sigma_1\rangle\\
&+ \frac{1}{\tau}[\langle J\rangle - \tanh(\beta)\langle\sigma_1\rangle]. && (59)
\end{aligned}$$

In fact, the new term $[\langle J\rangle - \tanh(\beta)\langle\sigma_1\rangle]$, the source of the conditional reflex, is a learning term as it couples the slow channel $(\langle J\rangle, \langle\sigma_1\sigma_2\rangle)$ with the fast one $(\langle\sigma_1\rangle, \langle J\sigma_2\rangle)$.
We can now start studying the dynamics in this regime by considering the sub-dynamics of ($\langle J\rangle$, $\langle\sigma_1\rangle$, $\langle\sigma_1\sigma_2\rangle$, $\langle J\sigma_2\rangle$), whose dynamical system reads off as

$$\begin{aligned}
\tau\frac{d\langle\sigma_1\rangle}{dt} &= -\langle\sigma_1\rangle + \tanh(\beta)\langle J\sigma_2\rangle, && (60)\\
T\frac{d\langle J\rangle}{dt} &= -\langle J\rangle + \tanh(\beta)\langle\sigma_1\sigma_2\rangle, && (61)\\
\tau\frac{d\langle\sigma_1\sigma_2\rangle}{dt} &= -2\langle\sigma_1\sigma_2\rangle + \tanh(\beta)\langle J\rangle + \langle\sigma_1\rangle, && (62)\\
\frac{d\langle J\sigma_2\rangle}{dt} &= -\frac{1}{\tau'}\langle J\sigma_2\rangle + \frac{1}{\tau}\langle J\rangle + \frac{1}{T}\tanh(\beta)\langle\sigma_1\rangle. && (63)
\end{aligned}$$

The associated matrix can be written as

$$\begin{pmatrix} 1/\tau & 0 & 0 & -\tanh(\beta)/\tau \\ 0 & 1/T & -\tanh(\beta)/T & 0 \\ -\frac{1}{\tau} & -\frac{1}{\tau}\tanh(\beta) & \frac{2}{\tau} & 0 \\ -\frac{1}{T}\tanh(\beta) & -\frac{1}{\tau} & 0 & \frac{1}{\tau'} \end{pmatrix}.$$

We cab diagonalize the dynamics and look for solutions as linear combinations as $Y(t) = a\langle\sigma_1\rangle + b\langle J\rangle + c\langle\sigma_1\sigma_2\rangle + d\langle J\sigma_2\rangle$ associating to this variable its caracteristic timescale $\bar{\tau} \Leftrightarrow Y$ and proceed as for the former regime.
Skipping all the calculations for the sake of simplicity we report only the solution

$$\langle\sigma_1(t)\rangle = c_1x_1e^{-\frac{t}{\bar{\tau}_1}} + c_2x_1^{'}e^{-\frac{t}{\bar{\tau}_2}} + c_3x_1^{''}e^{-\frac{t}{\bar{\tau}_3}} + c_4x_1^{'''}e^{-\frac{t}{\bar{\tau}_4}},$$

$$\langle J(t)\rangle = c_1x_2e^{-\frac{t}{\bar{\tau}_1}} + c_2x_2^{'}e^{-\frac{t}{\bar{\tau}_2}} + c_3x_2^{''}e^{-\frac{t}{\bar{\tau}_3}} + c_4x_2^{'''}e^{-\frac{t}{\bar{\tau}_4}},$$

$$\langle\sigma_1(t)\sigma_2(t)\rangle = c_1x_3e^{-\frac{t}{\bar{\tau}_1}} + c_2x_3^{'}e^{-\frac{t}{\bar{\tau}_2}} + c_3x_3^{''}e^{-\frac{t}{\bar{\tau}_3}} + c_4x_3^{'''}e^{-\frac{t}{\bar{\tau}_4}},$$

$$\langle J(t)\sigma_2(t)\rangle = c_1x_4e^{-\frac{t}{\bar{\tau}_1}} + c_2x_4^{'}e^{-\frac{t}{\bar{\tau}_2}} + c_3x_4^{''}e^{-\frac{t}{\bar{\tau}_3}} + c_4x_4^{'''}e^{-\frac{t}{\bar{\tau}_4}},$$

all the x's being the component of the following eigenvectors $V_1 = (x_1, x_2, x_3, x_4)$, $V_2 = (x_1^{'}, x_2^{'}, x_3^{'}, x_3^{'})$, $V_3 = (x_1^{''}, x_2^{''}, x_3^{''}, x_3^{''})$, $V_4 = (x_1^{'''}, x_2^{'''}, x_3^{'''}, x_3^{'''})$:

$$\begin{aligned} x_1 &= \frac{1}{\tau}\tanh(\beta), \\ x_2 &= \frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} - \sqrt{\Delta}\Big), \\ x_3 &= \frac{1}{\tau}\tanh(\beta), \\ x_4 &= \frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} - \sqrt{\Delta}\Big), \end{aligned}$$

$$\begin{aligned} x_1^{'} &= \frac{1}{\tau}\tanh(\beta), \\ x_2^{'} &= \frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} + \sqrt{\Delta}\Big), \\ x_3^{'} &= \frac{1}{\tau}\tanh(\beta), \\ x_4^{'} &= \frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} + \sqrt{\Delta}\Big), \end{aligned}$$

$$\begin{aligned} x_1^{''} &= \frac{1}{\tau}\tanh(\beta), \\ x_2^{''} &= \frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} + \sqrt{\Delta}\Big), \\ x_3^{''} &= \frac{T}{\tanh(\beta)}\Big[\frac{3}{2\tau T} - \frac{1}{2T^2} - \frac{1}{\tau^2} - \frac{1}{\tau T}\tanh^2(\beta) - \sqrt{\Delta}(\frac{1}{\tau} - \frac{1}{2T})\Big], \\ x_4^{''} &= -\frac{1}{2}\Big(\frac{1}{\tau} - \frac{1}{T} + \sqrt{\Delta}\Big), \end{aligned}$$

$$
\begin{aligned}
x_1^{'''} &= \frac{1}{\tau}\tanh(\beta),\\
x_2^{'''} &= \frac{1}{2}\Big(\frac{1}{\tau}-\frac{1}{T}-\sqrt{\Delta}\Big),\\
x_3^{'''} &= \frac{T}{\tanh(\beta)}\Big[\frac{3}{2\tau T}-\frac{1}{2T^2}-\frac{1}{\tau^2}-\frac{1}{\tau T}\tanh^2(\beta)-\sqrt{\Delta}(\frac{1}{\tau}-\frac{1}{2T})\Big],\\
x_4^{'''} &= -\frac{1}{2}\Big(\frac{1}{\tau}-\frac{1}{T}+\sqrt{\Delta}\Big),
\end{aligned}
\tag{64}
$$

Δ being $1/\tau^2+1/T^2+2(2\tanh^2(\beta)-1)/(\tau T)$.
The remaining sub-dynamics of $(\langle\sigma_2\rangle,\langle J\sigma_1\rangle,\langle J\sigma_1\sigma_2\rangle)$ is depicted by the system

$$\tau\frac{d\langle\sigma_2\rangle}{dt} = -\langle\sigma_2\rangle+1, \tag{65}$$

$$\tau'\frac{d\langle J\sigma_1\rangle}{dt} = -\langle J\sigma_1\rangle+\langle\sigma_2\rangle, \tag{66}$$

$$\frac{d\langle J\sigma_1\sigma_2\rangle}{dt} = -\frac{1}{\tau''}\langle J\sigma_1\sigma_2\rangle+\frac{1}{\tau}\langle J\sigma_1\rangle+\frac{1}{\tau'}\tanh(\beta). \tag{67}$$

By applying the framework previously shown several times we obtain the solutions

$$
\begin{aligned}
&\langle\sigma_2\rangle = c_1e^{-\frac{t}{\tau_1}}+1,\\
&\langle J\sigma_1\rangle = c_1\frac{T}{\tau'}e^{-\frac{t}{\tau_1}}+c_2e^{-\frac{t}{\tau_2}}+1,\\
&\langle J\sigma_1\sigma_2\rangle = c_1\frac{T}{\tau}e^{-\frac{t}{\tau_1}}+c_2e^{-\frac{t}{\tau_2}}+c_3e^{-\frac{t}{\tau_3}}+\tau''\left[\frac{1}{\tau}+\frac{1}{\tau'}\tanh(\beta)\right].
\end{aligned}
$$

6.3 Regime $s_1=\infty, s_2=\infty$: Two infinite signal.

Let us start with the following conditions: $s_1=\infty, s_2=\infty$, then we have $a_1=a_2=1, b_1=b_2=0$) and the evolution of the system can be written as

$$
\begin{aligned}
&T\frac{d\langle J\rangle}{dt} = -\langle J\rangle+\tanh(\beta)\langle\sigma_1\sigma_2\rangle,\\
&\tau\frac{d\langle\sigma_1\rangle}{dt} = -\langle\sigma_1\rangle+1,\\
&\tau\frac{d\langle\sigma_2\rangle}{dt} = -\langle\sigma_2\rangle+1,\\
&\tau\frac{d\langle\sigma_1\sigma_2\rangle}{dt} = -2\langle\sigma_1\sigma_2\rangle+\langle\sigma_1\rangle+\langle\sigma_2\rangle,\\
&\frac{d\langle J\sigma_1\rangle}{dt} = -\frac{1}{\tau'}\langle J\sigma_1\rangle+\frac{1}{T}\tanh(\beta)\langle\sigma_2\rangle+\frac{1}{\tau}\langle J\rangle,\\
&\frac{d\langle J\sigma_2\rangle}{dt} = -\frac{1}{\tau'}\langle J\sigma_2\rangle+\frac{1}{T}\tanh(\beta)\langle\sigma_1\rangle+\frac{1}{\tau}\langle J\rangle,\\
&\frac{d\langle J\sigma_1\sigma_2\rangle}{dt} = -\frac{1}{\tau''}\langle J\sigma_1\sigma_2\rangle+\frac{1}{T}\tanh(\beta)+\frac{1}{\tau}\langle J\sigma_2\rangle+\frac{1}{\tau}\langle J\sigma_1\rangle,
\end{aligned}
$$

whose solutions, in complete analogy with the previous introduced methodology, can be obtained as

$$\langle \sigma_1(t) \rangle = c_2 e^{-\frac{t}{\tau}} + 1, \tag{68}$$

$$\langle J(t) \rangle = c_1 e^{-\frac{t}{\tau}} + (c_2 + c_3)\frac{\tanh(\beta)}{T(\frac{1}{T} - \frac{1}{\tau})} e^{-\frac{t}{\tau}} + c_4 \frac{\tanh(\beta)}{T(\frac{1}{T} - \frac{2}{\tau})} e^{-\frac{2t}{\tau}} + \tanh(\beta), \tag{69}$$

$$\langle \sigma_2(t) \rangle = c_3 e^{-\frac{t}{\tau}} + 1, \tag{70}$$

$$\langle \sigma_1(t)\sigma_2(t) \rangle = (c_2 + c_3) e^{-\frac{t}{\tau}} + c_4 e^{-\frac{2t}{\tau}} + 1, \tag{71}$$

$$\langle J(t)\sigma_1(t) \rangle = c_1 e^{-\frac{t}{T}} + \frac{\tanh(\beta)}{(\frac{1}{T} - \frac{1}{\tau})}(\frac{c_2}{\tau} + \frac{c_3}{\tau}) e^{-\frac{t}{\tau}} + c_4 \frac{\tanh(\beta)}{\tau T(\frac{1}{T} - \frac{2}{\tau})(\frac{1}{T} - \frac{1}{\tau})} e^{-\frac{2t}{\tau}} + c_5 e^{-\frac{t}{\tau'}} + \tanh(\beta), \tag{72}$$

$$\langle J(t)\sigma_2(t) \rangle = c_1 e^{-\frac{t}{T}} + \frac{\tanh(\beta)}{(\frac{1}{T} - \frac{1}{\tau})}(\frac{c_2}{\tau} + \frac{c_3}{\tau}) e^{-\frac{t}{\tau}} + c_4 \frac{\tanh(\beta)}{\tau T(\frac{1}{T} - \frac{2}{\tau})(\frac{1}{T} - \frac{1}{\tau})} e^{-\frac{2t}{\tau}} + c_6 e^{-\frac{t}{\tau'}} + \tanh(\beta), \tag{73}$$

$$\langle J(t)\sigma_1(t)\sigma_2(t) \rangle = 2c_1 e^{-\frac{t}{T}} + \frac{\tanh(\beta)}{\tau(\frac{1}{T} - \frac{1}{\tau})}(c_2 + c_3) e^{-\frac{t}{\tau}} + c_4 \frac{\tanh(\beta)}{\tau^2(\frac{1}{T} - \frac{2}{\tau})(\frac{1}{T} - \frac{1}{\tau})} e^{-\frac{2t}{\tau}} + \tag{74}$$

$$+ \quad c_7 e^{-\frac{t}{\tau''}} + \tanh(\beta) + (c_5 + c_6) e^{-\frac{t}{\tau'}} + \tanh(\beta). \tag{75}$$

$$\tag{76}$$

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