Synaptic Scaling Improves the Stability of Neural Mass Models Capable of Simulating Brain Plasticity

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10 **Running title:** Improving Neural Mass Models

Abstract: Neural mass models offer a way of studying the development and behaviour of large-scale brain networks through computer simulations. Such simulations are currently mainly research tools but as they improve, they could soon play a role in understanding, predicting and optimising patient treatments, particularly in relation to effects and outcomes of brain injury. To bring us closer to this goal we took an existing state-of-the-art neural mass model capable of simulating connection growth through simulated plasticity processes. We identified and addressed some of the model's limitations by implementing biologically plausible mechanisms. The main limitation of the original model was its instability, which we addressed by incorporating a representation of the mechanism of synaptic scaling and ex-

22 aminating the effects of optimising parameters in the model. We show that the
23 updated model retains all the merits of the original model, while being more
24 stable and capable of generating networks that are in several aspects similar
25 to those found in real brains.

26 **Keywords:** brain networks, plasticity, synchronisation, development, in-
27 juries, synaptic scaling

1 Introduction

Brain networks share with many other natural and technological networks, features of short path lengths, high clustering and a modular architecture featuring *hubs* (brain regions that are on a high proportion of the shortest paths between other brain regions). These characteristics are features of the central nervous system of various organisms, from *C. elegans* to humans (Reijneveld, Ponten, Berendse, & Stam, 2007; Sporns, 2016) and are seen both in structural and functional networks; and at both the microscopic (Bonifazi et al., 2009; Yu, Huang, Singer, & Nikolić, 2008) and macroscopic scales (Hagmann et al., 2008).

One way to study the emergence of such structure is via computer modelling. Neural mass modelling (NMM) is a popular computational approach (Ponten, Daffertshofer, Hillebrand, & Stam, 2010; Stam, Hillebrand, Wang, & Van Mieghem, 2010; Stam, Pijn, Suffczynski, & Lopes da Silva, 1999; Ursino, Zavaglia, Astolfi, & Babiloni, 2007) that reduces computational complexity by treating large populations of neurons collectively as neural “masses” and simulating whole-brain behaviour as interactions between masses at this level. Using a NMM, Stam *et al.* (2010) showed that a network of coupled neural masses can develop a modular architecture through an interaction between two processes – growth dependent plasticity (GDP) and synchronisation dependent plasticity (SDP). GDP represents the creation of new long-range structural connections between nodes in an unconstrained, distance-dependent manner (Kaiser, Hilgetag, & Van Ooyen, 2009). SDP models the creation of structural connections between nodes displaying time-correlated

neural activity. Stam *et al.* found that only a balanced combination of both processes resulted in networks with modular architectures similar to those found in brain.

Because of the parallels between the biologies of development and repair after injury (S. Cramer & Chopp, 2000), a biologically-plausible model of how plasticity supports development could also have clinical application in modelling of recovery after brain injury. The most common forms of acquired brain injury are traumatic brain injury (e.g. after motor vehicle accidents) and stroke: archetypes respectively of diffuse multi-focal; and (typically large) focal injury patterns. Understanding the biology of brain repair and reorganisation after brain injuries remains incomplete. In particular, although a considerable amount is known in general terms about the repertoire of biological processes potentially available after injury (S. C. Cramer *et al.*, 2011), our current inability to understand the potential for recovery in individual cases is a barrier to improving outcomes (Castellanos *et al.*, 2011; Dancause & Nudo, 2011; Zeiler & Krakauer, 2013).

Network neuroscience perspectives (Fornito, Zalesky, & Bullmore, 2016; Sporns, 2016) have been applied to brain injury and have led to a recognition of the importance of hub preservation in determining the effects of injuries on network integrity (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009). An understanding is required of how injury distributions affect capacity for reorganisation after injury, so that rate-limiting steps in an individual patient's recovery pathway (potential therapeutic targets) can be identified. Such an understanding will require, amongst other things, a whole-brain, systems level understanding of reorganisation after injury.

77 In this study we took Stam *et al.*'s existing NMM (2010) and analysed
78 its limitations with particular respect to modelling effects of injury, and ex-
79 tended it to incorporate representations of additional important processes.
80 We show the behaviour of the modified model is in several ways more bi-
81 ologically plausible at the macroscopic scale than the original model, and
82 demonstrate its potential clinical application with real-world connectomes.

83 2 Methods

84 2.1 The Original Neural Mass Model

85 We build upon the previous research conducted by Lopes da Silva *et al.* (1974)
86 and Stam *et al.* (2010). Lopes da Silva *et al.* developed a NMM where each
87 of the neural masses generates an EEG or MEG like signal while Stam *et al.*
88 introduced plasticity processes to that model.

89 In the NMM the average membrane potentials ($V_e(t)$ and $V_i(t)$) and pulse
90 densities ($E(t)$ and $I(t)$) characterise the behaviours respectively of the ex-
91 citatory and inhibitory populations of neurons in each mass. Pulse densities
92 define the portion of cells firing per time step and are related to their corre-
93 sponding membrane potentials with static non-linear functions $S_e(V_e(t))$ and
94 $S_i(V_i(t))$. The excitatory and inhibitory post-synaptic potentials (EPSPs and
95 IPSPs respectively) are modelled by the $h_{e1}(t)$, $h_{e2}(t)$ and $h_i(t)$ impulse re-
96 sponses. Coupling from excitatory to inhibitory populations and vice-versa
97 depends also on the coupling constants C_{ei} and C_{ie} , values for which are
98 drawn from work by Lopes da Silva *et al.* (1974). Neural masses are also

99 excited by an outside input signal $P(t)$.

100 Following Stam *et al.* the neural masses are coupled together. Coupling
101 is always reciprocal and excitatory. Together with the external input, the
102 previous outputs of coupled neural masses are also used as the excitatory
103 impulses (Ursino et al., 2007):

$$i_e(t) = P(t) + \mu \cdot \sum_{j \in M} (w_{ij}(t) \cdot E_j(t - \Delta t)), \quad (1)$$

104 where M is the set of all neural masses, and w_{ij} is the strength of the
105 connection between neural masses i and j . In Stam *et al.*'s original model
106 $E_j(t - \Delta t)$ is the excitatory pulse density of neural mass j in the previ-
107 ous update step. In our upgraded model we incorporate distance-dependent
108 propagation delay (see section Propagation delay). $P(t)$ is the outside input
109 signal, drawn from a normal distribution:

$$P(t) = \mathcal{N}(P \cdot \Delta t, 0.1^2), \quad (2)$$

110 where P represents sub-cortical input, and Δt is the discrete time step.

111 The excitation and inhibitory impulse responses are calculated as in
112 Zetterberg *et al.*'s study (Zetterberg, Kristiansson, & Mossberg, 1978). The
113 impulse responses over time are implemented as a convolution in the discrete
114 time domain. The calculated responses are then used to find membrane
115 potentials. The average excitatory membrane potential is calculated as:

$$h_{1,e1}(t) = e^{a_e \Delta t} \cdot h_{1,e1}(t - \Delta t) + i_e(t), \quad (3)$$

$$h_{2,e1}(t) = e^{b_e \Delta t} \cdot h_{2,e1}(t - \Delta t) + i_e(t), \quad (4)$$

$$h_{1,i}(t) = e^{a_i \Delta t} \cdot h_{1,i}(t - \Delta t) + i_i(t), \quad (5)$$

$$h_{2,i}(t) = e^{b_i \Delta t} \cdot h_{2,i}(t - \Delta t) + i_i(t), \quad (6)$$

$$V_e(t) = (A_e \cdot (h_{1,e1}(t) - h_{2,e1}(t))) - (A_i \cdot (h_{1,i}(t) - h_{2,i}(t))). \quad (7)$$

116 In the equations above A_e and A_i are the excitatory/inhibitory ampli-
 117 tudes, and a_e , b_e , a_i , b_i are excitatory/inhibitory shape parameters. $i_i(t)$ is
 118 the inhibitory impulse:

$$i_i(t) = C_{ie} \cdot I(t). \quad (8)$$

119 A similar process is used to calculate the inhibitory membrane potential:

$$h_{1,e2}(t) = e^{a_e \Delta t} \cdot h_{1,e2}(t - \Delta t) + i_{ei}(t), \quad (9)$$

$$h_{2,e2}(t) = e^{b_e \Delta t} \cdot h_{2,e2}(t - \Delta t) + i_{ei}(t), \quad (10)$$

$$V_i(t) = A_e \cdot (h_{1,e2}(t) - h_{2,e2}(t)). \quad (11)$$

120 $i_{ei}(t)$ is the excitatory/inhibitory impulse, calculated as:

$$i_{ei}(t) = C_{ei} \cdot E(t). \quad (12)$$

121 The sigmoid functions relating the average membrane potential to pulse
122 densities are also taken from Zetterberg *et al.* (1978):

$$E(t) = S_e(V_e(t)) = \begin{cases} g \cdot e^{q \cdot (V_e(t) - V_{de})} \cdot \Delta t, & \text{if } V_e(t) \leq V_{de} \\ g \cdot (2 - e^{q \cdot (V_{de} - V_e(t))}) \cdot \Delta t, & \text{otherwise,} \end{cases} \quad (13)$$

$$I(t) = S_i(V_i(t)) = \begin{cases} g \cdot e^{q \cdot (V_i(t) - V_{di})} \cdot \Delta t, & \text{if } V_i(t) \leq V_{di} \\ g \cdot (2 - e^{q \cdot (V_{di} - V_i(t))}) \cdot \Delta t, & \text{otherwise,} \end{cases} \quad (14)$$

123 where g and q are parameters of the sigmoid function that relate mem-
124 brane potential to impulse density, while V_{de} and V_{di} are threshold potentials
125 used in the sigmoid function that relate membrane potential to impulse den-
126 sity for main population of excitatory or inhibitory neurons. Since the jus-
127 tification about the choice of activation functions and values of parameters
128 used in them cannot be explained briefly and we feel like a longer explanation
129 is out of the scope of this manuscript we invite readers interested in these
130 details to consult Zetterberg *et al.*'s research (1978).

131 Coupling between two neural masses is shown schematically in Figure 1
132 and details of model parameters are listed in Table 1.

133 Stam *et al.* simulate structural brain plasticity using two processes –
134 growth dependent plasticity (GDP) and synchronisation dependent plasticity

Table 1: **A description and values of all the parameters used in the NMM.**

Parameter	Description	Value
T	Number of steps	200000, 400000
Δt	Update step	0.002 s
N	Number of neural masses	32, 90
P	Sub-cortical input level	550 spikes/s
A_e	EPSP amplitude	1.6 mV
a_e	EPSP shape parameter	55 s ⁻¹
b_e	EPSP shape parameter	605 s ⁻¹
A_i	IPSP amplitude	32 mV
a_i	IPSP shape parameter	27.5 s ⁻¹
b_i	IPSP shape parameter	55 s ⁻¹
g	Membrane potential to impulse density	25 s ⁻¹
q	Membrane potential to impulse density	0.34 mV ⁻¹
V_{de}	Threshold potential for excitatory neurons	7 mV
V_{di}	Threshold potential for inhibitory neurons	7 mV
C_{ei}	Excitatory-inhibitory connection strength	32
C_{ie}	Inhibitory-excitatory connection strength	3
μ	Coupling strength factor	4
a_{ss}	Synaptic scaling strength factor	2
a_{sdp}	SDP step size	0 – 0.0002
b_{sdp}	Hill function steepness parameter	2
h_{sdp}	Value for which SDP function changes sign	1
n_d	Steps in correlation calculation	20
a_{gdp}	GDP step size	0.00001
c_{gdp}	Distance dependent strength decay	0.2
η_{gdp}	GDP randomness	[-1, 1]
n_f	Number of injured nodes in focal injuries	8
p_f	Probability of edge injury in focal injuries	0.75
t_0	Clamping threshold	0.05

Figure 1: **Presentation of two coupled neural masses in a NMM.** Inside each neural mass are two populations, a population of excitatory (pyramidal) neurons, and a population of inhibitory neurons. Blue squares in the figure mark processes associated with excitation, while red squares visualise inhibitory processes. The state of each neural mass is modelled by its average membrane potentials $V_e(t)$ and $V_i(t)$ and pulse densities $E(t)$ and $I(t)$. Membrane potentials are converted to pulse densities with sigmoid functions (S_e and S_i). Pulse densities are converted to membrane potentials by impulse responses ($h_{e1}(t)$, $h_{e2}(t)$, and $h_i(t)$). C_{ei} and C_{ie} are constants that determine the coupling strength between the excitatory and inhibitory populations of neurons. Two masses are coupled via excitatory connections by a delay t_d – the excitatory output of coupled neural masses in one of the previous update steps is used as an excitatory input of the observed neural mass in the current update step. Along with excitation from coupled neural masses. $P(t)$ simulates pulse densities coming from thalamic sources.

135 (SDP) (Stam et al., 2010). GDP simulates a distance-dependent connectivity
 136 with neural masses that are closer to each other more likely to form strong
 137 connections than those that are further away:

$$\Delta w_{ij}(t) = a_{gdp} \cdot \Theta(w_{ij}(t) - e^{c_{gdp} \cdot d_{ij}}) \cdot \eta_{gdp}. \quad (15)$$

138 Here, w_{ij} is the connection strength between neural masses i and j , a_{gdp}
 139 is the GDP step size, c_{gdp} determines the decay rate, η_{gdp} is a random number

140 (uniform distribution) on the $[-1, 1]$ interval, and d_{ij} is the distance between
 141 neural masses i and j . In Stam's original model this is an integer taken
 142 from the interval $[1, N/2]$, with N the number of neural masses and circular
 143 boundary conditions:

$$d_{ij} = \begin{cases} |i - j|, & \text{if } |i - j| \leq \frac{N}{2} \\ \frac{N}{2} - |i - j|, & \text{otherwise.} \end{cases} \quad (16)$$

144 $\Theta(x)$ is the modified Heaviside function:

$$\Theta(x) = \begin{cases} 1, & \text{if } x < 0 \\ -1, & \text{otherwise.} \end{cases} \quad (17)$$

145 The second plasticity component is SDP, which strengthens connection
 146 weights between two neural masses if they are synchronised (show correlated
 147 firing), and decreases them if they are not. If two nodes are not connected
 148 ($w_{ij} = 0$) then SDP cannot establish a new connection. SDP is described
 149 with a Hill function:

$$\Delta w_{ij}(t) = a_{sdp} \cdot \left(\frac{r_{ij}(t)}{r_{ij}(t) + h_{sdp}^{b_{sdp}}} - \frac{1}{2} \right), \quad (18)$$

150 where a_{sdp} is the SDP step size, h_{sdp} determines where the Hill function
 151 changes its sign, b_{sdp} is the steepness parameter. The value for the b_{sdp}
 152 parameter was based on the exploratory analysis about how this parameter
 153 influences the behaviour of the model. The desired behaviour is achieved
 154 by setting the parameter's value to 2 [C.J. Stam, *personal communication*,
 155 October, 2019]. $r_{ij}(t)$ measures the correlation between excitation of neural

156 mass i and neural mass j at time step t :

$$r_{ij}(t) = (c_{ij}(t) + 1)^{b_{sdp}}, \quad (19)$$

157 where $c_{ij}(t)$ is Pearson’s correlation between firing of neural masses i and
 158 j ($E_i(t)$ and $E_j(t)$), computed over the preceding n_d time steps.

159 Following Stam *et al.* our model first performs SDP, followed by GDP. Af-
 160 ter both components of plasticity are calculated all connections are clamped
 161 to a $[0, 1]$ interval:

$$w_{ij}(t) = \begin{cases} 0, & \text{if } w_{ij}(t) < 0 \\ 1, & \text{if } w_{ij}(t) > 1 \\ w_{ij}(t), & \text{otherwise.} \end{cases} \quad (20)$$

162 The original Stam model generates connections with extremely low weights
 163 not seen in “real world” clinical structural connectomes. This may reflect gen-
 164 uine absence of such weak connections or an inability of current methods such
 165 as diffusion tensor imaging to identify them. To improve the clinical validity
 166 of our analyses we set very low edge weights ($<$ clamping threshold t_0) to
 167 zero before evaluating generated structural networks’ properties.

168 **2.2 Our enhancements**

169 To increase the biological relevance of the original NMM, we upgraded it by
 170 implementing two mechanism that seem to be present in real brain – synap-
 171 tic scaling and more realistic propagation delay. Propagation delay models
 172 the delay that is required for impulse of one neural mass to reach another

neural mass. Synaptic scaling is a homeostatic mechanism and should as such increase the stability of the model, this is important since instability is one of the main issues of the original Stam model (see section 3.1).

Synaptic Scaling

Stam *et al.*'s modelling of activity-dependent plasticity via SDP emphasises long-range, activity dependent, changes in structural connectivity between nodes. This would correspond to plasticity mechanisms *in vivo* primarily involving white matter. Although activity- and learning-dependent changes in the physico-chemical properties of white matter have been described (Drikkoningen *et al.*, 2015; Johansen-Berg, 2012, 2007; Sampaio-Baptista *et al.*, 2013), *in vivo* views of plasticity conventionally emphasise *grey matter* changes located at the synapse (i.e. at a much smaller spatial scale than the neural mass). We modified the Stam *et al.* model to incorporate representation of these processes via synaptic scaling. Even though network sizes, strength and number of synaptic connections, and connection architecture may all vary substantially between brain regions, excitation/inhibition balance and oscillation regimes across them are maintained (Barral & Reyes, 2016). Neuronal activity levels are adjusted by a plasticity mechanism that adjusts synaptic strengths in a way that promotes stability (Barral & Reyes, 2016; Turrigiano & Nelson, 2004), a process we refer to here as *synaptic scaling*. In their computational study Hellyer *et al.* (Hellyer, Jachs, Clopath, & Leech, 2016) showed that incorporation of synaptic scaling into computational models increases the resemblance of simulated functional connectivity networks to their empirical counterparts. Vattikonda

197 *et al.* (Vattikonda, Surampudi, Banerjee, Deco, & Roy, 2016) also suggest
 198 that synaptic scaling might play an important role in restoration of func-
 199 tional connectivity after a brain injury. Thus, we enhanced the model by
 200 implementing synaptic scaling.

201 Our implementation of synaptic scaling is based on Barral and Reyes’
 202 finding that synaptic scaling is correlated with the quantity of neural connec-
 203 tions (Barral & Reyes, 2016). With synaptic scaling equation 1 in our model
 204 becomes:

$$i_e(t) = (P(t) + \sum_{j \in M} w_{ij} \cdot E_j(t - \Delta t)) \cdot SS_i(t). \quad (21)$$

205 $SS_i(t)$ represents the synaptic scaling factor of the observed neural mass
 206 (neural mass i) at the current time step, and is calculated as:

$$SS_i(t) = \frac{a_{ss}}{\sqrt{1 + k_i(t)}}, \quad (22)$$

207 where a_{ss} is the synaptic scaling strength factor, and $k_i(t)$ the sum of all
 208 observed neural mass’ connections in the current time step:

$$k_i(t) = \sum_{j \in M} w_{ij}(t). \quad (23)$$

209 **Propagation Delay**

210 In their model Stam *et al.* incorporated a *fixed* propagation delay between
 211 neural masses (t_d) of one update step. As a result a neural mass always
 212 uses the previous excitation of all other connected neural masses as its cou-
 213 pled excitatory input, regardless of their distance. However, since SDP uses

214 correlation of oscillations between nodes to modify structural connections
 215 which may be very sensitive to such propagation delays, we incorporated
 216 distance-dependent propagation times.

217 Wang *et al.* (Wang et al., 2008) reported a conduction time of myelinated
 218 white matter axons to be at most 5 ms ($t_c = 0.005s$). Based on this, the
 219 propagation delay between masses (i, j) is in our model calculated as:

$$t_d = \left\lceil d_{ij} \cdot \frac{t_c}{d_{max} \cdot \Delta t} \right\rceil, \quad (24)$$

220 where d_{max} is the maximal distance between two nodes, which as per Stam
 221 *et al.* is the number of nodes in the network divided by two ($N/2 = 16$).

222 2.3 Measured metrics

223 Network properties were quantified using standard metrics calculated using
 224 the Brain Connectivity Toolbox (Rubinov & Sporns, 2010).

- 225 • Characteristic path length is the average shortest path between all pairs
 226 of nodes, it is a commonly used measure of network integration (Watts
 227 & Strogatz, 1998).
- 228 • Clustering coefficient is a simple measure of segregation. Local cluster-
 229 ing coefficient is calculated as the fraction of triangles around an indi-
 230 vidual node (Watts & Strogatz, 1998). The mean clustering coefficient
 231 for the network hence reflects the prevalence of clustered connectivity
 232 around individual nodes.
- 233 • Weighted modularity represents another measure of network segrega-

tion (Newman, 2004; Rubinov & Sporns, 2010). Networks with high modularity have dense connections between the nodes within same modules and sparse connections between nodes in different modules.

- Assortativity coefficient is a measure of network resilience to injury. Networks with a positive assortativity coefficient usually have a resilient core of mutually interconnected hubs, and are likely to be able to maintain functional connectivity by rerouting, while those with a negative assortativity coefficient usually have widely distributed and vulnerable hubs (Newman, 2002).

2.4 Simulations

Preliminary simulations showed that networks converged to the same mature networks irrespective of the starting network connectivity chosen (e.g. random or maximal connection strengths). For simplicity empty, connection-less networks were used as the starting point for all simulations.

Figure 2 visualises the phases of our simulations through the characteristic path length metric. During the first, “development” phase (phase **A** in Figure 2), the network matures and converges to a stable, developed state. In simulations of brain injury, an instantaneous injury event at $t = 200000$ was followed through a “recovery phase” (**B** in Figure 2) for a further 200000 steps.

Figure 2: **Visualisation of the biphasic simulations** – with an initial “development” phase (**A**), and post-injury “recovery” phase (**B**). All data analysis is conducted after the network stabilises at the end of phase **A**. The graph shows that (in this case) the characteristic path length has stabilised before the end of the development phase. The moment of injury is clearly visible as a transient in the observed metric at the beginning of the recovery phase. A focal injury was used in the visualized simulation, the visualisation would look almost the same in the case of a diffuse injury.

254 2.5 Injuries

255 We incorporated simple representations of focal and diffuse brain injuries. Fo-
256 cal injuries have a particular location and typically arise from vascular insults
257 such as stroke. Diffuse injuries are more distributed. A common example
258 is the diffuse axonal injury that arises in high-energy collisions (e.g. motor
259 vehicle accidents). Actual impact of the brain with an external structure
260 is not necessary: injury occurs because tissue types with varying densities
261 accelerate/decelerate at different rates (Gennarelli & Graham, 2005).

262 We represent focal injuries in the model by damaging structural connec-
263 tions of n_f nodes. Edges belonging to injured nodes have a probability of
264 injury of p_f . We apply diffuse injuries by damaging structural connections of
265 all nodes, to have comparable severity of injuries the probability of an edge
266 injury in diffuse injury is calculated as:

$$p_d = p_f \cdot \frac{n_f}{N}. \quad (25)$$

267 If an edge is flagged as injured, the severity of its injury is drawn from
268 $N(0.75, 0.25)$. The calculated severity is then subtracted from the strength
269 of developed edges (set to 0 if the new value is negative). An example of
270 both focal and diffuse injuries applied to a developed network is shown in
271 Figure 3.

Figure 3: **Application of a focal and a diffuse injury to a developed network.** Example of application of a focal injury (top-middle) and a diffuse injury (bottom-middle) to a developed network (left) resulting in the injured network (top-right for focal and bottom-right for diffuse injury).

3 Results

3.1 Instability of the Original Model

We identified an important limitation when applying the Stam *et al.*'s original model in a macroscopic setting; individual connection weights never truly stabilise (see Figure 4 and Figure 5). Although not a concern for the specific purposes of that report, such continuing variability in structural connectivity on a macroscopic scale is of dubious biological plausibility.

Our analysis of how various parameters shape the behaviour of Stam *et al.*'s original model showed that its instability arises mainly from excessive

281 plasticity processes (high values of a_{sdp} and a_{gdp}). We calculated the insta-
 282 bility of the model from the variance of edge weights after the “development”
 283 phase completed, which represents a timepoint at which underlying connec-
 284 tome should have stabilised. Instability of the model was thus evaluated
 285 between times 200000 and 400000 and defined as the maximum value from
 286 the set of edge instabilities. Instability of a particular edge was calculated as
 287 the difference between the maximum and minimum value of the edge weight
 288 during these 200000 steps. Since edge weights range from 0 to 1, maximum
 289 instability of an edge and consequently the model equals to 1. The analysis
 290 was conducted on following parameter intervals: $a_{sdp} = [0.01, 0.0001]$ and
 291 $a_{gdp} = [0.001, 0.00001]$, we ran the simulation 10 times for each parameter
 292 pair to account for the variability due to stochastic processes. Influence of
 293 a_{sdp} and a_{gdp} on the instability of the model is visualised in Figure 4. Fig-
 294 ure 5 compares the instability of an edge in Stam *et al.*’s and our model, the
 295 visualisation shows that re-tuned SDP and GDP parameters and synaptic
 296 scaling greatly decrease the instability of the model.

297 **3.2 Synaptic Scaling**

298 Synaptic scaling is a homeostatic mechanism and should as such promote the
 299 stability of the model. To validate this we incorporated the mechanism into
 300 Stam *et al.*’s model (2010) and explored how the intensity of synaptic scaling
 301 (the a_{ss} parameter) influences the stability of the model. We used Stam *et*
 302 *al.*’s original values for plasticity parameters ($a_{sdp} = 0.01$ and $a_{gdp} = 0.001$),
 303 which as we have already shown (Figure 4) cause extreme instability. The

Figure 4: **A visualisation of Stam *et al.*'s model's instability.** Graph illustrates effects of a_{sdp} and the a_{gdp} on model instability, where a value of 1 represents maximum instability (shaded band indicates 95% CI). The instability of the model was measured when the model should have already “developed”, however edge weights of models with high instability keep on changing their values dramatically, which is not biologically plausible. The original Stam *et al.* model used a_{sdp} values around 0.01 and an a_{gdp} of 0.001.

analysis was conducted on a $[0.1, 4]$ interval for the a_{ss} parameter, we ran the simulation 10 times for each parameter value to account for variability due to stochastic processes. Our results show that when the strength of synaptic scaling is low to medium stability is indeed improved. When the strength of synaptic scaling is too high then the model again becomes unstable (see Figure 6). This occurs because even small changes in connection weights trigger huge changes in the strength of input impulses of neural masses, leading to abrupt transitions in the behaviour of neural masses. Based on these findings we set the synaptic scaling strength parameter (a_{ss}) in our simulations to 2, a value large enough for synaptic scaling to have a significant influence on the behaviour of the model without extremely erratic behaviour.

Figure 5: **A comparison of connection weight stability between two random nodes in our enhanced (blue) and the original Stam *et al.* (red) models** A period of 2000 update steps following the initial development period of 200 000 steps is shown. Connections in the enhanced network are stable, while in Stam *et al.*'s model they never truly stabilise (only a single connection is shown here, but the finding is seen in all connections). Note here that this visualisation does not compare the instability of the whole model, as seen in Figure 4, but the connection weight of two random edges. The instability of Stam *et al.*'s model equals 1, while the instability of our model in this experiment equalled 0.02 (95% CI, 0.017 to 0.027).

315 Introduction of synaptic scaling markedly altered the dynamics of the
316 NMM. Since recent studies suggest that brain operates near criticality, i.e.
317 near a bifurcation point (Cocchi, Gollo, Zalesky, & Breakspear, 2017) we
318 re-tuned model parameters in order to achieve the same in our model. Nodes
319 exhibited unhealthy oscillation when the coupling strength between neural
320 masses (μ) was over 4 (Figure 7). Setting $\mu = 4$ leads to nodes operating
321 near the bifurcation point. The result are nodes producing an EEG-like
322 signal (Figure 8).

Figure 6: **Influence of synaptic scaling on the model's stability.** Synaptic scaling promotes model stability at low to medium values of the synaptic scaling strength parameter (a_{ss}). Points indicate actual measurements, with the loess smoother line and its 95% CI interval shown.

3.3 Injuries

To analyse both types of injuries in more detail we used our model to construct 10 developed networks. We then applied a focal and a diffuse injury to each developed network independently and used the previously described metrics (see section 2.3) to examine the difference between both types of injuries. The largest difference between both injuries was in the characteristic path metric, here a focal injury caused a much larger disruption to the underlying network than a diffuse injury. This suggest that focal injuries greatly reduce integration of a network. Similar, but not as prominent, results can be seen on the assortativity coefficient metric, which measures the network's ability to reroute and lessen the impact of injuries. When looking at metrics that measure the segregation of the network (clustering coefficient and

Figure 7: **Parameter scan showing regions of node oscillations.** Nodes operate near the bifurcation point when the value of the coupling strength parameter μ is ≈ 4 .

335 weighted modularity) the difference between two types of injuries was not
 336 very large and could be attributed to the random nature of the experiment.
 337 For a visualization of this findings see Figure 9.

338 Preliminary simulations suggested that the type of injury (focal or diffuse)
 339 does not influence the results in injury based experiments found later in the
 340 manuscript. Because of this and for the sake of brevity these experiments
 341 are based solely on focal injuries.

342 **3.4 Comparison with Networks Generated by the Orig-** 343 **inal Model**

344 In this section we study 32-node synthetic networks to facilitate comparison
 345 of the behaviour of our enhanced model with Stam *et al.*'s original findings
 346 (Stam et al., 2010). The model enhancements are described in detail in

Figure 8: **Signal generated by nodes in the model.** Nodes/neural masses in NMMs produce an EEG-like signal. Due to an injury of exaggerated severity all nodes switch to an unhealthy oscillating regime after the injury, this occurred at the 200000th time step.

347 previous sections, for details about re-parametrization in order to increase
 348 the model’s stability see section 3.1, for details about synaptic scaling and
 349 propagation delay see section 2.2.

350 When only GDP processes are active ($a_{sdp} = 0$) simulations result in net-
 351 works with distance dependent connection strengths, but no degree correla-
 352 tions and weak modularity (top left network in Figure 10). The introduction
 353 of SDP gives rise to complex networks with small-world features and modular
 354 structure confirming Stam *et al.*’s conclusion that both GDP and SDP are
 355 required to generate this complexity (Figure 10).

356 The original and our enhanced models show very similar recovery-phase
 357 behaviour as reflected by structural whole-network metrics – after an injury
 358 occurs the networks regrow damaged connections and metrics partially nor-
 359 malise (Figure 2). However introducing synaptic scaling has important effects

Figure 9: **Comparison between focal and diffuse injuries.** Focal injuries cause a larger disturbance in the network regarding its integration (the characteristic path metric) and its resilience (the assortativity coefficient metric). The differences between both types of injuries in terms of network segregation (clustering coefficient and weighted modularity metrics) are not as prominent and could be accounted to the random nature of our experiment.

on network dynamics and patterns of functional activity, as reflected in analysis of $E(t)$. The enhanced model shows a peak in the power spectrum at $\approx 10\text{Hz}$ comparable to physiological EEG data (Murias, Webb, Greenson, & Dawson, 2007) (see the top left chart on Figure 11) with emergence of higher-frequency harmonics after injury. Stam *et al.*'s model's dynamics show little reaction to injury (Figure 11). This finding holds in both the case of a focal and a diffuse injuries.

3.5 Comparison to a Real World Connectome

In this subsection we apply the modified model to human MRI connectivity datasets to examine the clinical validity of the model's generated networks. To do this we first derived a real-world network using the DSI studio software to perform diffusion MRI tractography. As underlying data we used the

Figure 10: **Effect of GDP and SDP on network developed by our enhanced model.** Only the presence of both GDP and SDP results in network with small-world features similar to those of neural networks in our brains. Graphs visualizing values of observed metrics depict the mean value of the metric (solid line) and its 95% CI (shaded area).

372 HCP-842 population averaged template and overlaid the tracts with regions
 373 of interest in the AAL parcellation in standard space. Next, we investigated
 374 if our modified model is capable of synthesising networks similar to real brain
 375 structural connectomes, as judged by characteristic path length, clustering
 376 coefficient, weighted modularity, and assortativity coefficient metrics.

377 Since the “real world” connectome we used for comparison has $n = 90$
 378 nodes, and since increasing n increases the amount of coupling excitation, we

Figure 11: **Power spectrum features** Figures show the FFT power spectrum of activity ($E(t)$) for a single highly-injured node over 50000 step periods before and immediately after injury. In both the enhanced (left) and original Stam (right) models, GDP and SDP are operative throughout (i.e. connection strengths are changing during the 50000 step periods). In Stam *et al.*'s case, the power spectrum is almost the same after the injury as it was before. The enhanced model adds synaptic scaling and shows distinctly different post-injury behaviour.

379 changed the coupling strength factor (μ) to ensure neural masses continued
 380 to operate near the bifurcation point. An analysis analogous to Figure 7
 381 found that $\mu = 3$ was optimal for a 90 node network to avoid unhealthy
 382 oscillation. We also modified the parameters that govern the behaviour of
 383 plasticity processes. We fixed $a_{gdp} = 0.00001$ as before and adjusted the
 384 other three plasticity parameters – a_{sdp} , b_{sdp} , and c_{gdp} . To keep the values of
 385 plasticity metrics comparable to Stam *et al.* and the first part of our study,
 386 we again set the maximum distance d_{max} to 16.

387 Figure 12 shows that the modified model is indeed capable of generat-
 388 ing networks with topologies (as reflected by global metrics) comparable to

389 healthy adult connectomes. In the healthy “real world” structural connec-
 390 tome used for comparison, the values for characteristic path length, clustering
 391 coefficient, weighted modularity, and assortativity coefficient were 4.15, 0.19,
 392 0.35, and 0.03 respectively. The synthesised networks’ properties are most
 393 similar with $a_{sdp} = 0.0004$, $b_{sdp} = 12$, and $c_{gdp} = 0.3$; resulting in values of 5.3,
 394 0.16, 0.36, and 0.0004 for characteristic path, clustering coefficient, weighted
 395 modularity, and assortativity coefficient respectively.

Figure 12: **Comparison between the topologies of a “real world” healthy clinical connectome and networks derived with our model.** Comparison metrics were calculated on networks derived using the following parameter intervals: $a_{sdp} = [0.0003, 0.0006]$, $b_{sdp} = [10, 18]$, and $c_{gdp} = [0.2, 0.4]$. Dotted grey lines visualise values of measured metrics in the “real world” network.

396 4 Conclusion

397 We have confirmed that an enhanced version of Stam *et al.*’s original model
 398 (2010) retains important characteristics of the original model including the

399 generation of networks with modular, small-world features. We had two con-
400 cerns with the original model relevant to our use case of modelling clinically
401 realistic connectomes' responses to injury. The first was the instability of
402 connection weights (Figure 5). We managed to stabilise connections by in-
403 troducing synaptic scaling and re-tuning parameter values in accordance to
404 this change.

405 The second and more fundamental concern relates to the biological plau-
406 sibility of SDP as a mechanism of brain plasticity. SDP represents activity-
407 dependent strengthening of long-range *structural* connectivity between nodes.
408 Although practice- and learning-dependent changes in the physicochemical
409 properties of white matter (as demonstrated by MRI) are increasingly recog-
410 nised and described (Drijkoningen et al., 2015; Johansen-Berg, 2012, 2007;
411 Sampaio-Baptista et al., 2013) the biology these changes represent remains
412 unclear (Assaf, Johansen-Berg, & Thiebaut de Schotten, 2017; Johansen-
413 Berg, Baptista, & Thomas, 2012). It is assumed that clinical recovery after
414 brain injury in large part reflects re-establishment of *functional* connectivity
415 *despite* persistently disrupted structural connectivity (i.e. re-establishment
416 of functional connectivity via indirect pathways, for which hub integrity is
417 important). We wanted to incorporate a representation of the processes that
418 are much more widely accepted to be part of brain activity-dependent plas-
419 ticity mechanisms that operate at a much smaller spatial scale. Synaptic
420 scaling is a process of synapse-level regulation of balance between excitatory
421 and inhibitory activity in neural networks (Roy et al., 2017). It promotes sta-
422 ble oscillating regimes in nodes regardless of the coupling input they receive.
423 Implementation of synaptic scaling not only helped with the stabilisation of

the model but it also changed the dynamics of the model’s behaviour after injury (Figure 11). Note that we followed Stam *et al.* in using a window of 20 time steps (n_d) when calculating SDP. This means that SDP is only shaped by activity that happened in the last 20 time steps, or 0.033 seconds. The biological interpretation of this is that only activity in the gamma frequency bands is influencing structural plasticity in this model.

An initial goal in our work was to simulate recovery and evolution of connectivity in clinically-derived connectomes after traumatic brain injury. Instead of injuring networks that had converged to stability *de novo* we wanted to use real injured-patient structural networks as the starting point and then simulate their ongoing recovery/evolution. Although we confirmed that our NMM produced networks with similar global characteristics to clinically-sourced networks (Figure 12) this was unsuccessful as the patient connectome is not the converged end-result of the model’s own connectivity-evolving processes. Additionally we had hypothesised we might observe the *hypersynchrony* phenomenon – a temporary increase in time-domain correlation of spatially-distributed brain regions – that has been described as a general response to brain injury and pathology (Hillary & Grafman, 2017). However this model does not replicate this phenomenon (data not shown), leaving its biological basis unclear. Nevertheless we believe further study of NMMs incorporating representations of these and related biological processes have the potential to increase understanding of the complex relationships between structural and functional connectivity after injury (Goñi et al., 2014; Hillary & Grafman, 2017; Tewarie et al., 2018).

448 **Author Contributions**

449 R.F. developed the study idea and supervised the study. J.D. implemented
450 the model, ran the simulations and analysed the results. Both authors dis-
451 cussed the results and contributed to the final manuscript.

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458 **Data Availability Statement**

459 All the data supporting this study and the model's source code (model is
460 coded in Matlab, visualisations and analysis were conducted with R) are
461 publicly available on GitHub (<https://github.com/demsarjure/NMM>).

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