BIOLOGICAL SIMULATIONS BY AUTONOMOUS AGENTS: TWO EXAMPLES USING THE NETLOGO ENVIRONMENT.

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Abstract

Simulation of complex biological events by autonomous agents is particularly convenient whenever: i) the events depend on both time and space, and ii) some collective, organized trends emerge at the population level from a few simple properties characterizing each single agent. This has been exemplified by simulating two quite different phenomena, namely: i) the distribution of cod populations in the North Atlantic ocean, and ii) the synchronous activation of brain neurons occurring in many neurological disorders, including epyleptic seizures.

In both cases simulations of the observed time dependent trends, although qualitative,provided hints to work out relevant mechanistic hypotheses.

Introduction

The collective dynamics arising from the behaviour of various kinds of living entities encouraged in recent years the design of specific simulation environments, from the molecular to the ecological level (9), particularly in the study of metabolic and genetic systems (12; 6). In our opinion, among such environments special attention deserves NetLogo (1), a general purpose, programmable modeling tool for natural and social phenomena, authored by Uri Wilensky in 1999 at Northwestern University (Evanston, IL). NetLogo is endowed, among other things, with a straightforward portability over different platforms and operating systems, and the tackled simulation problems span from math and computer science to earth scienc and even art.

In this preliminary account we refer about simulations carried out in ecological and neurological contexts. In the former case we tried and reproduce the distribution of cod stocks in the North Atlantic Ocean, associated to hemoglobin phenotypes in the blood of the various stocks (10), as confirmed by a recent biochemical approach (5). In the latter case, we modeled the typical electric activity patterns occurring in the central nervous systems as the result of an epileptic crisis, through the activations of a number of agents which synchronize their own activity cycle.

```
to reproduce
ask-concurrent turtles
[
 if (count turtles > MaxCodsNr) [stop]
 if breed = codHb11s  and  (ReproField11_1 > (Random 5) or ReproField11_1 > (Random 5))  [ hatch 1  ]
 if breed = codHb22s  and  (ReproField22_1 > (Random 5) or ReproField22_2 > (Random 5))  [ hatch 1  ]
 if breed = codHb12s  and  (ReproField12_1 > (Random 5) or ReproField12_2 > (Random 5))  [ hatch 1  ]
]
end

to fishery
ask patches
  [if (FisheryFields > Random 100)  [ASK TURTLES-HERE [ die ] ] ]
end
```

```
to go
 set ActiveNeurons count turtles with [color = yellow]
 ask turtles  [
    if Energy < 0
        [set clock random (round cycle-length) set Energy (InitEnergy)]
  increment-clock
    if  (clock > window) and (clock >= threshold)
        [set Energy (Energy + 0.004)  set ActiveSynapses  count turtles in-radius (Radius) with [color = yellow]
    if ActiveSynapses >= MinActiveSynapses
        [set clock reset-level ]
    ifelse (ActiveNeurons / TotalNeurons) > 0.95
        [set Energy (Energy - 1)]
    [if (count redneurons with [color = yellow] / (red_neurons)) > 0.95
        [set Radius abs (MaxRadius * InitEnergy / (mean [Energy] of turtles))] ] ]
 recolor  ]
 do-plot
 tick-advance 1
end
```

FIGURE 1. *Examples of NetLogo code.* The upper and lower panels include the crucial fragments of the code used to work out, respectively, the simulation of the cod stocks distribution and of the neuronal activation, discussed in this paper. Notice the straightforward implementation, through appropriate 'if' statements, of the basic control structures in both cases, namely: the reproduction and death of cods, and the energy–regulated synchronization of neurons. In particular, the last "if" statement includes the dependence of the synchronization ability of each neuron according to an expression of the general form: $SynchronizationAbility = f(Radius)/f(Energy)$, where $Radius$ quantifies the extent of the circular region within which active neighbouring neurons may be sensed and depending, in turn, upon the available metabolic $Energy$.

In both cases, the connection between the micro-level behavior of individuals and the macro-level patterns that emerge from their interaction, could be easily explored thanks to the peculiar features of the NetLogo environment.

EXAMPLE 1: DISTRIBUTION OF COD STOCKS IN THE NORTH ATLANTIC AREA

In the attempt to simulate the geographical distribution of cod stocks in the North Atlantic, we considered two hemoglobin phenotypes, corresponding to the Hb11 and Hb22 homozygotes, and preferring higher and lower temperatures, respectively. A third

phenotype, corresponding to the heterozygote Hb12, was also considered, and taken as temperature-insensitive.

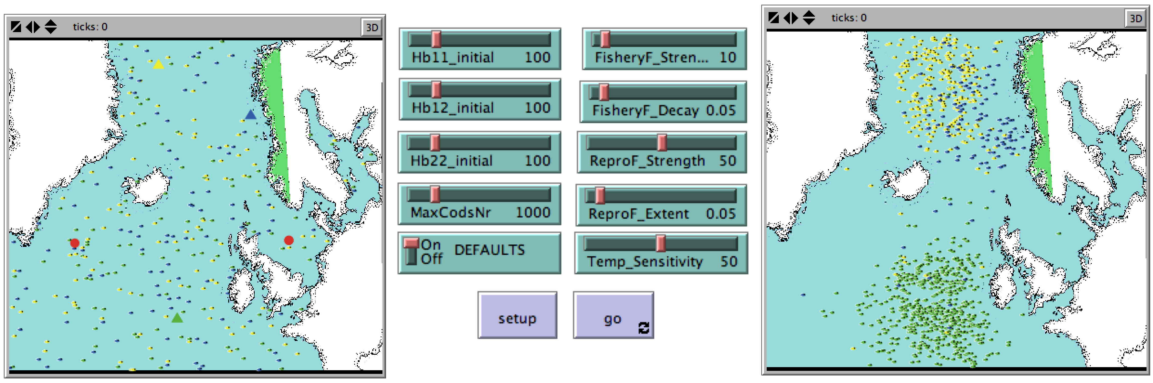


FIGURE 2. *Simulation set-up for the distribution of cod stocks in the North Atlantic.*
Central Panel: the sliders in the first column define the initial number of individuals, up to 1000, for each phenotype $Hb11..$, $Hb22..$, $Hb12..$, as well as the maximum number $MaxCodNr$, up to 10000, of individuals of any phenotype sustainable by the environment. Deactivating the bottom switch, $DEFAULTS$, allows substitution of predefined with user-defined values. In the second column, sliders control the intensity and decay constant for the Reproduction, $ReproF$, and Fishery, $FisheryF$, fields. The allowed range (0 – 100 and .1 – .01, respectively) is in arbitrary units. The location of the reproduction fields for the three stocks are indicated by the triangles of the corresponding color (visible in the left panel); red circles indicate the location of fishery fields. Notice that both type of fields can be placed everywhere on the map. The last slider in the column is for the temperature sensitivity coefficient (0 – 100, arbitrary units) of the Hb11 and Hb22 phenotypes as well as for the attraction exerted by the norwegian coast (deep green in the map) on the Hb12 phenotype. The North Atlantic map in the middle panel is visualized by the Setup button, which also initializes all the variables to the default values. The *Go* button is used to start/pause the simulation, respectively.
Left and Right Panels show the distribution of cod stocks (Hb11 = green, Hb22 = yellow, Hb12 = blue) at time = 0 and after about 500 (arbitrary) time units (see figure 4 for the whole time course). Notice, in the right panel, the clustering of the three phenotypes in different areas. The simulation was paused when the total number of fishes reached the maximum allowed value (1000).

Assuming that the ocean temperature increases linearly with decreasing latitude, the individuals of the Hb11 (red) and Hb22 (yellow) phenotypes, initially distributed at random in the ocean (Fig. 2, left panel), will move towards South or North according to their temperature preference, while the Hb12 heterozygote will be attracted by the norwegian coast (see Figure 2).

Birth and death of fishes may occur with a probability reaching a maximum in specific "hot spots" and exponentially decreasing with distance from such spots, as in the

presence of a sort of Reproduction- and Fishery-Force-Fields, according to the following expression:

$$FI = FImax * \exp(-dC * D) \quad (1)$$

where FI = FieldIntensity; $FImax$ = Maximal FieldIntensity; dC = Decay Constant; D = Distance from the corresponding "hot spot", where FImax applies. The total number of the three phenotypes will in no case superseed a given "sustainable" ($MaxCodsNr$) amount. The location of the hot spots for Reproduction and Fishery Fields may be predefined on the map by appropriate sliders in the input/output control panel(see Figure 2).

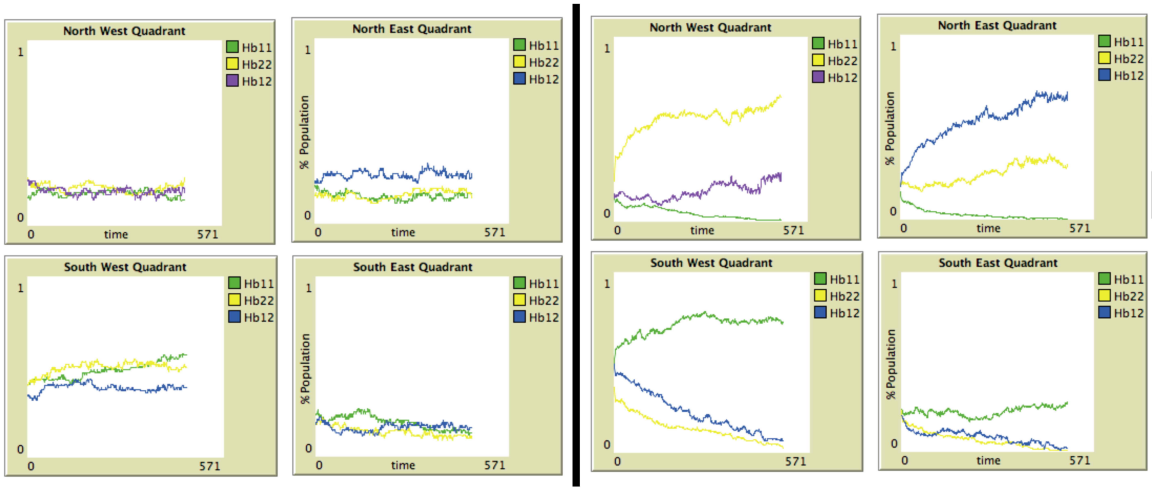


FIGURE 3. *Time course of simulated cod stocks distribution in North Atlantic.* The four panels in both sides refer to the fractional abundance of the three considered phenotypes (Hb11, Hb22 and Hb12) in the four quadrants associated to the map in Fig. 2 (the 0,0 point halfway from Iceland and Scotland). All simulations used the parameters shown in Figure 2 and identical initial conditions, except the Temperature Sensitivity (See the Text and the *TempSensitivity* slider in Figure 2) which was set to 0 and 50 (arbitrary units) in the left and right panels, respectively.

Even the simplest model aiming to reproduce the distribution of cod stocks in North Atlantic should take into account the existence of adaptive correlation between phenotypes and natural (primarily temperature and salinity) as well as anthropic (primarily fishery and pollution) factors, in agreement with the available information (10). We simulated the effect of the former type of variables by including in the set of properties characterizing any individual fish: i) a propensity to migrate Southwards or Northwards, respectively, for Hb11 and Hb22 homozygotes, and Eastwards, towards the norwegian coast, for the heterozygotic (Hb12) individuals, ii) a propensity to better reproduce in one or two areas, specific for each phenotype. At present, such areas were arbitrarily selected in the aim to couple the known temperature/salinity regimes of the North Atlantic areas and the heterogeneous preferences of the various stocks. The anthropic factors are

more difficult to be accounted for, due to the large heterogeneity of their time and space dependence. We condensed their influence in up to three so called 'fishery fields', of arbitrary intensity and location (See Fig. 2), causing an aspecific death of fishes of any phenotype.

Example 2: Synchronizing brain neurons

In this case, we represented brain neurons in terms of identical, autonomus agents randomly distributed in a brain-shaped bidimensional space (see figure 4), and switching between an active and a nonactive state in a completely independent (randomic) fashion.

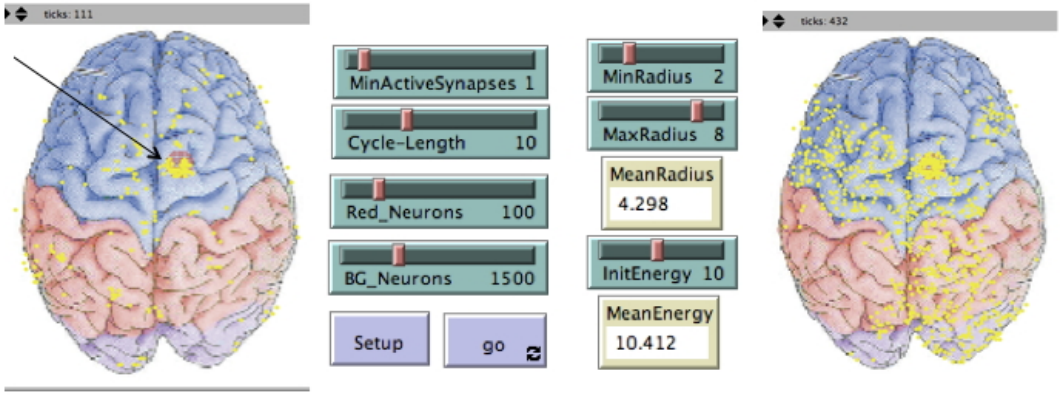


Figure 4. *Simulation set-up for synchronized brain neurons.*
Middle section: the first column contains the sliders which define the total number of neurons in a small, high density region, indicated by the arrow (Red_Neurons), and in the light blue and pink remaining regions of the brain surface (BackGround: BG_Neurons). Notice that in the side panels only the active neurons at a given instant are visualized as yellow dots. Other two sliders control the length of the activity cycle of each neuron and the minimum number of active neighbours it must sense in order to synchronize. The second column contains the sliders (MinRadius and MaxRadius) limiting the length of the window within which each neuron may sense the activity of the others. It also contains the slider for the initial level of the metabolic energy, quickly depleted during syncrhonous activity and restored during normal activity. The two small panels report the actual, instantaneous value of the above parameters, throughout the whole simulation.
The left and right panels visualize the activation state of neurons on the brain surface after 111 and 432 time bits from the beginning of the simulation. Notice that in the left panel only the neurons of the high density (red) region appear as partially synchronized; after a while (right panel), synchronization extended to a large fraction of neurons in the whole brain.

In order to qualitatively reproduce the dynamics of epileptic seizures, we assumed that neuron populations become synchronized since each neuron tries and match its own activity cycle with that of other neurons in the neighborhood. A necessary prerequisite, then, is that it can 'sense' a minimum number of active neurons within defined spatial and

temporal windows. Moreover, since keeping synchronized is a strong energy–consuming activity, it looks reasonable that a synchronized status should be limited by the metabolic energy level of the tissue. Our model accounts for that in so far as the energy level influences the maximal distance at which a neuron may sense other neurons: the lower the energy, the shorter such distance, and hence the lower the chance to get synchronized (see Fig. 5 and Fig.1).

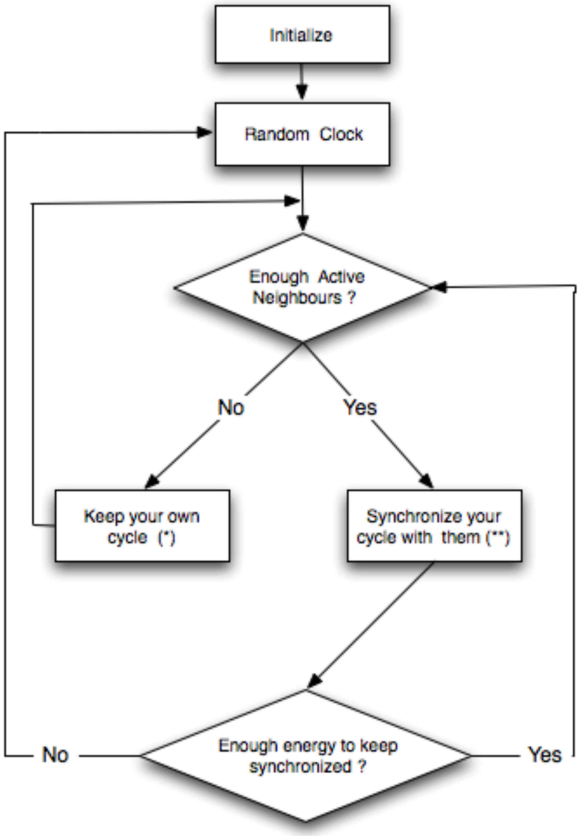
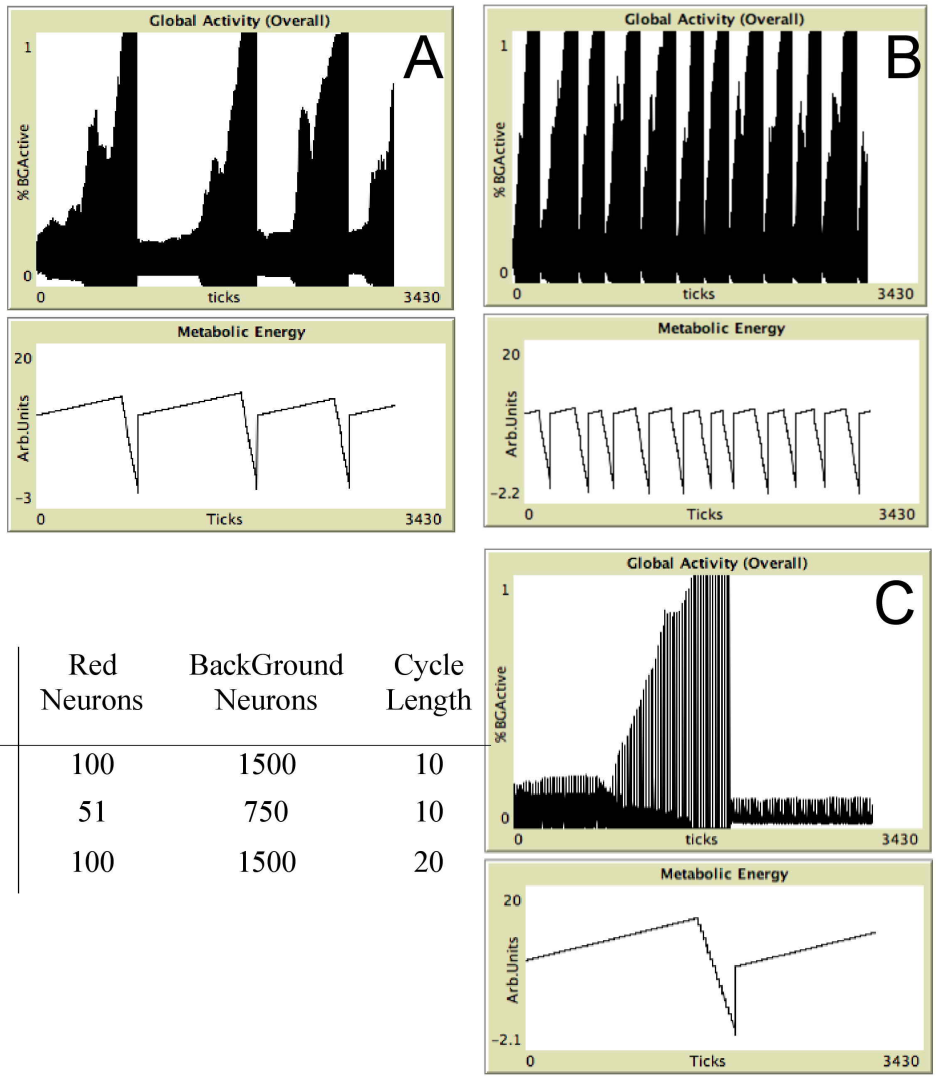


FIGURE 5. *Block diagram of the neurons' synchronization rule.*

A variety of synchronized activation patterns may soon be observed if each single neuron is influenced by the number of active neurons in its surroundings. More specifically, if regions of different size and neurons' density are distinguishable in the brain, assuming that each neuron may interact with other neurons within a given radius, at least two different types of interactions can be foreseen: among neurons of the same or of different regions. An interesting consequence is that, if neurons within a small region easily synchronize due to their high density, they may also act as triggers of synchronous activity over the whole brain, thus reproducing the role of the so called "epileptic focus"(7).

We could set up a system in which: i) very simple 'agents' simulate neurons, and ii) synchronous activation is assumed to depend upon the ability of single neurons to



	Red Neurons	BackGround Neurons	Cycle Length
A	100	1500	10
B	51	750	10
C	100	1500	20

FIGURE 6. *Time course of simulated synchronous activation of brain neurons.* Simulations in the A, B, C panels were all carried out according to the conditions detailed in Fig. 4, but for the values listed in the lower-left table. Notice how the frequency of the activity bursts, at difference with the overall shape, is very sensitive to the neurons density (panels A,B) as well as to the length of the activity cycle of single agents (panel A,C). The latter may be defined as the maximum time length between two subsequent active state in the absence of synchronization. It is also noticeable the dramatic drop of the metabolic energy as a consequence of the massive synchronization within the activity bursts.

switch from a 'resting' to an 'active' state at a given instant within their activity-cycle. Thus, under resting conditions the activation of single neurons occurs randomly within the activity-cycle; it may occur, however, that synchronous activation emerges in the

neurons' universe (brain) as a result of an autocatalytic process where more and more neurons become active at the same time.

Figure 6 shows the time-courses corresponding to the interplay of the apparently most relevant variables which regulate the synchronus activation, namely the neurons density in a given brain region, and the length of the activity cycle of each single neuron. Notice that the time units, here as in all our simulations, correspond to the time required by the environment to update the state of the whole set of agents. No provision has been taken to scale the arbitrary time units since, at the present stage of our qualitative simulations, what matters is the occurrence of the considered phenomena relative to each other.

Discussion

In many cases, the smooth learning-curve and the captivating user interface of the interpreted NetLogo environment counterbalance its non-astonishing number-crunching power and make it well suited to exploratory modeling and qualitative predictions. Even more so in the presence of a high number of variables, as in the study of ecological and nervous systems, where a wide spectrum of conditions has to be considered for an optimal design of experimental validations.

In our opinion, among the most significant features of NetLogo remains the ability to easily account for both time and space dependent events. The properties of single agents at a given time, in fact, may also depend upon the free moving in a non-homogeneous environment, where any location is endowed with specific features. Simulating cod distribution in the North Atlantic took full advantage of that, since we assumed that: i) preferential directions of fish moving reflect latitude-related temperature sensitivity, and ii) local fish density reflects the relative location of central-symmetric force fields representing reproduction or lethal (fishery) areas.

While Fig. 4 provides a glimpse of the performance in the qualitative description of fishery resources, its full exploitation in a possibly predictive context, however, is still out of reach. A major problem here lies in both the variability of environmental information and the scarcity of biological data. On the former side, detailed information on the temperature and salinity regimes in different North Atlantic regions of the type shown in Fig. 7 (left panel), would be most appropriate, due to the direct influence on the oxygen availability and hence on the energetic metabolism of marine species. However, the strong and rapid alterations of seasonal temperature cycles, ice-melting and ocean salinity levels induced by global warming, has enormously amplified the uncertainty of any prediction in these fields. On the biological side, after the seminal studies on cod phenotypes distribution in the North Atlantic ocean by Sick (10), only in recent years our knowledge on cod physiology and genetics has significantly improved (5).

Another impressive level of performance/simplicity ratio reached by NetLogo is in the simulation of interactions among agents based upon geometrical or functional links giving rise to extensively synchronized behaviour [1]. In reproducing the emergence of

[1]It is interesting to note that an analogous task faced by a traditional simulation tool requires considerably deeper theoretical and programming involvement (8; 11). Moreover, as for flexibility and simplicity/power ratio, NetLogo compares favourably also with general-purpose environments of similar type, like V-lab (3) or StarLogo (2)

ordered, synchronized patterns of activity in a population of initially independent neurons, we were initially inspired by a model called 'fireflies' included in the rich NetLogo model library (13). Our scheme, however, besides being based upon stationary, instead of moving – like in the previous case of cod stocks –, agents, contains a number of original features, primarily the energy-linked switch between a 'synchronized' and an 'asynchronized' state for each neuron. In this first attempt to reproduce the occurrence of epileptic seizures (4), we set up a minimal mechanistic scheme in which the ability to get synchronized is restricted to contiguous neurons, that is within a circular region of variable radius. An alternative scheme able to provide activity patterns (Figure 7, right panel) even more similar to actual epileptic EEG signals [2], may be designed according to the same approach followed in the cod stock distribution case, namely assuming the agents freely moving in some central-symmetric force-fields. It looks quite difficult, however, to reconcile the latter scheme to any established physiological evidence.

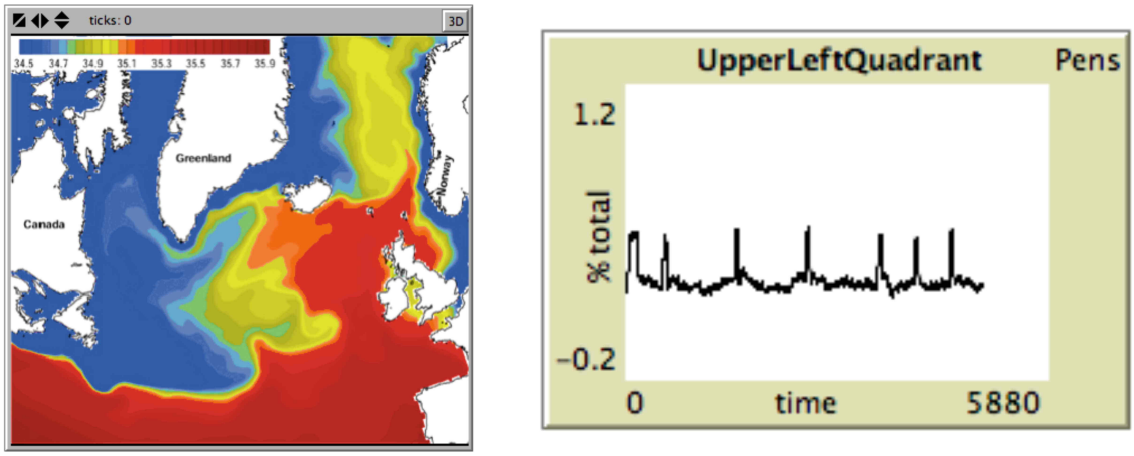


FIGURE 7. *Towards more quantitative simulations.* The left panel shows the false-color map of salinity levels in the North Atlantic. Such data, taken together with the associated thermoclines, are very important for any reliable simulation of cod stock distributions in the ocean: as specified in the text, however, the main difficulty here is the experimental validation of the model's predictions. The right panel concerns a neuronal synchronized activity we worked out within the same simulation environment but using a slightly different model than that described here. Although less realistic, such a model provides a better fit to actual EEG recordings (see also the text).

A more promising evolution of our model should be in tracing the preferential channels (functional links) for the mutual activation of neurons in discontinuous, distant regions in the brain space. Such a network-like scheme could provide a useful modelistic counterpart to the well known existence of specific pathways connecting distant regions in the brain, which become active as the result of several pathological/physiological events. Moreover, it could also benefit of the considerable refinements recently gathered

[2]See Panuccio et al. Fig 1B, Fig 2A, in this same issue

by topologically-oriented networks in modeling other biological activity patterns of huge complexity, like gene-expression or metabolic-activity patterns. (6; 12)

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References

[1] http://ccl.northwestern.edu/netlogo/.
[2] http://education.mit.edu/drupal/starlogo-tng.
[3] http://vlab.unm.edu/html/software.html.
[4] Commission on epidemiology and prognosis: Guidelines for epidemiologic studies on epilepsy. *Epilepsia 34*, 4 (1993), 592–596.
[5] Brix, O., Thorkildsen, S., and Colosimo, A. Temperature acclimation modulates the oxygen binding properties of the atlantic cod (gadus morhua l.) genotypes - hbi*1/1, hbi*1/2, and hbi*2/2 - by changing the concentrations of their major hemoglobin components. *Comp. Biochem. Physiol. Part A 138* (2004), 241–251.
[6] De Jong, H. Modeling and simulation of genetic regulatory systems: a literature review. *J. Comput. Biol. 9* (2002), 69–105.
[7] Fisher, R., van Emde, B. W., Blume, W., Elger, C., Genton, P., Lee, P., and Engel, J. Epileptic seizures and epilepsy: definitions proposed by the international league against epilepsy (ilae) and the international bureau for epilepsy (ibe). *Epilepsia 46* (2005), 470–472.
[8] Mirollo, R., and Strogatz, S. Synchronization of pulsed-coupled biological oscillators. *SIAM Journal of Applied Mathematics 50*, 6 (1990), 1645–1662.
[9] Russell, S., and Norvig, P. *Artificial Intelligence: A Modern Approach.* Prentice-Hall, 1995.
[10] Sick, K. Haemoglobin polymorphism of cod in the baltic and the danish belt sea. *Hereditas 54*, 1 (1965), 19–48.
[11] Strogatz, S., Mirollo, R., and Matthews, P. Coupled nonlinear oscillators below the synchronization threshold: relaxation by the generalized landau damping. *Physical Review Letters 68*, 18 (1992), 2730–2733.
[12] Tu, B. P., and McKnight, P. Metabolic cycles as an underlying basis of biological oscillations. *Nature 7* (2006), 697–701.
[13] Wilenski, U. Netlogo fireflies model. *http://ccl.northwestern.edu/netlogo/models/Fireflies* (1998).