Discussion on the “Dynamic model to conceptualize multiple environmental pathways to the epidemic of Chronic Kidney Disease of unknown etiology (CKDu)”

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Abstract

Jayasinghe et al. [Science of the Total Environment, 705 (2020) 135766] propose a ‘dynamical’ model of Chronic Kidney Disease of Unknown etiology (CKDu) wherein CKDu arises as an emergent property of a complex system where they claim that weak multiple environmental factors contribute. They criticize the usual approaches as being “reductionist”. We use their model as a basis of a discussion on the possibility of treating CKDu as an emergent property resulting from the interaction of multiple weak environmental factors with the organism. The model does not reveal anything beyond what is already known from simple considerations of well-known feedback loops, but has the merit of re-stating those issues in a different format. If a proper weighting of the possible environmental factors is included, most proposed environmental factors drop out and what Jayasinghe et al. call the “reductionist” approach naturally arises due to the weight of evidence. The theory that the consumption of water containing fluoride and magnesium ions as found in water from regolith aquifers drawn via house-hold wells is found to clearly hold within this model when proper weighting is included. However, we show by a counter-example that such models can be easily misused, leading to completely misleading conclusions. A response formalism useful in the theory of complex systems and emergent modes is presented in the context of the current problem. In addition to there being a lack of adequate data to fully implement such a theory, it is seen that such elaborations are unnecessary and misleading in the present context.

Keywords: Chronic kidney disease, CKDu, Systems approach, emergent properties, fluoride, ground water

1. Introduction

Jayasinghe et al. [1] begin their short communication with a review of the literature on chronic kidney disease of unknown etiology (CKDu) that affects tropical pastoral communities in many parts of the world stretching from meso-American countries like Ecuador, to Andhra Pradesh in India, El-Minia in Egypt...
and to villages scattered mainly in the north central province of Sri Lanka. While Ecuador is the most affected by CKDu, Sri Lanka has led the way in launching a concerted program of research into CKDu since 2008.

When CKDu caught the serious attention of researchers (in early work like 4, 5), it was natural to begin to look at well-known nephrotoxins like heavy metals (e.g., Cd, Pb, As etc.), pesticides, chlorohydrocarbon residues, or even dehydration of workers under field conditions as possibilities. The latter possibility has now been more or less eliminated in the context of Sri Lanka while the claimed presence of heavy-metal toxins in fish etc., could not be confirmed by subsequent work. Other possible causes, e.g., snake bite, algal toxins in drinking water, and synergistic action of geologically occurring fluoride ions together with magnesium ions found in hard water, fluoride acting synergistically with Na$^+$ ions or Al$^{3+}$ ions, glyphosate residues acting synergistically with arsenic and Ca$^{2+}$ ions, have been proposed.

Important controlling factors for the leaching of fluoride from groundwater aquifers are the presence of magnesium and bicarbonates, evapo-transpiration, and long contact times of water with the aquifer. The proposal that fluoride ions act synergistically with magnesium ions is based on experimental evidence for characteristic renal-tubular damage in the kidney observed in laboratory mice, as well as on the positions of fluoride and magnesium ions in the Hofmeister series. Supporting evidence based on Gibbs Free-energy calculations showing synergies between fluoride and magnesium ions is also available. The fluoride theory is also supported by the observation of skeletal fluorosis in many residents of endemic areas. The bicarbonate in hard water found in disease-endemic areas helps to leach fluorides from the regolith aquifers that supply the well water used by residents in endemic regions. These wells are not connected to the agricultural water table linked to water reservoirs (“tanks”) and irrigation works, as shown by isotopic tracer studies. Independent studies have shown a correlation of CKDu with groundwater usage. No CKDu is found in dry-zone farming areas like the Jaffna peninsula where the drinking water is located in limestone aquifers, while all other factors discussed by Jayasinghe et al. hold. Similarly, villages in the region that use water from natural springs are also free of CKDu. Rats fed with dug-well water from endemic areas developed renal damage. Fernando et al. have found higher levels of fluoride in serum and urine in endemic CKDu patients as compared with endemic control groups who live in high fluoride and hard water areas. Thus the fluoride-magnesium hypothesis has a strong experimental and theoretical basis.

Chronic kidney disease in Andra Pradesh is believed to be similar to Sri Lankan CKDu in its clinical characteristics. Hence its etiology may also be similar to Sri-Lankan Regolith Aquifer-Sourced Nephropathy (RASN), owing to similar geochemical characteristics in the two regions.

The common pre-conception that agrochemical residues and industrial products in the food chain (air, water, soil, food) may cause chronic diseases has good scientific underpinnings for sufficiently elevated doses of toxins and exposure to them. The environmental degradation arising from industrialization and the
need for intensive agriculture to feed an increasing demographic since World-War II are well recognized. The increasing use of herbicides like glyphosate since its introduction (in Sri Lanka circa 2000, and several years earlier to Indian agriculture) have been a matter of public concern. Hence, such considerations would be the first suspect in regard to the appearance of CKDu. However, such a hypothesis has not found experimental support. A review of the WHO-sponsored study [6], and other independent studies [19, 20] ultimately lead to the conclusion that agrochemical residues are below well established thresholds for chronic kidney disease of any kind.

In the case of glyphosate, in addition to the usual microbial degradation via the AMPA pathway, glyphosate is removed from the ecosystem and made into an insoluble, inert chelate [21] of essentially zero bioavailability due to the action of calcium ions (and similar chelating cations) found in the hard water of the endemic regions. The WHO-sponsored study [6] found no significant levels of glyphosate in biopsy studies of CKDu patients in 97% of the cases, while the 3% cases with glyphosate traces are within the error bars of such field studies. This is one reason why some researchers, dissatisfied by the conclusion that agrochemical residues seem to be not implicated, look for “synergies” among below-threshold amounts of residues as possibly leading to chronic epidemic effects. Alternatively, they measure the deactivated insoluble chelate in the sediments and soils and continue to claim that there is persisting “glyphosate” in the environment, although what is found is a very different (ceramic-like) substance, a polymeric N-(phosphonomethyl) glycinate, and not glyphosate. In fact, some researchers had already rushed to name the disease as an agricultural nephropathy.

On the other hand, contrary to the findings of most authors (e.g., [22, 20]) Jayalal et al. [23] claim to find significant above-threshold amounts of Pb and Cd (but not arsenic) in the diet of some 70-80 residents in CKDu-endemic villages that they studied. Furthermore, these authors have only studied cadmium or lead, and without simultaneously determining the concentration of antagonistic ions like zinc or selenium in the diet. Hence, such studies are likely to be totally inadequate for making conclusions about chronic toxicity. Furthermore, a common problem in such studies is that the ‘total cadmium’ determined via mass-spectroscopy is not the ‘bioavailable’ cadmium in the food. While other authors have also found Cd and other metal toxins in rice and vegetables (both in the endemic areas, and in other areas) [24, 6, 22, 26] their evaluations of typical diets did not lead to a conclusion about toxicity from the diet. Premaratna’s work [24] attempts to indicate total Cd as well as bioavailable values (about 30% of total Cd). If the individuals in the test sample of Jayalal et al. had indeed been affected by cadmium toxicity, in addition to it being reflected in the analytical data, more well established clinical signs of Cd toxicity [27] besides CKDu should have been evident, but no such supporting evidence is indicated in the report by Jayalal et al.

In Ref. [12] we argued that large rivers flowing from the agricultural regions of the tea plantations can bring down macro-nutrients like phosphates found in fertilizers, but this does not apply to the micro-components (e.g., cadmium) of
fertilizers, as shown in Sec. 2 of Ref. [26]. Such rivers flow into all parts of Sri Lanka while CKDu is restricted to regions with regolith aquifer-fed household wells.

In the case of Ecuadorian nephropathy, it should not be forgotten that oil extraction in Ecuador began in 1972 and became a major pillar of the economy. Millions of gallons of oil and toxic residues have been discarded directly onto the environment causing health and environmental issues [28]. Indeed, some 30 billion gallons of toxic wastes and crude oil had been discharged into the land and waterways of the Ecuadorian Amazon by 1993 [28]. In contrast, the use of agrochemicals is less widespread among the poor pastoral farming communities that use more traditional agriculture. Nevertheless, while agrochemicals like glyphosate have been targeted for ban by zealous activists opposed to genetically modified (GM) foods, little action has been taken against the oil and mining industries.

Thus, while some proposed causative factors have a good basis in experimental data, most others are unsubstantiated, even if strongly pushed by anti-GM activists. However, Jayasinghe et al. basically include these so-called causative factors irrespective of whether there is evidence for them in the traditional sense, e.g., via the Bradford Hill criteria [29], or within more modernized criteria (e.g., as discussed in [30]). The latter are increasingly incorporated into mathematical models and dynamic toxico-kinetic models. Such mathematical methods enable the researcher to carry out data integration from a variety of sources or causative agents, and use quantitative measures, e.g., for what Hill termed “strong” or “weak” associations.

2. The causative-pathways model for CKDu by Jayasinghe et al. [1]

Given that the publication of Jayasinghe et al. is a short communication, we may regard it as a declaration of intent for an upcoming more detailed study. Hence we propose to examine here the limitations of their preliminary formulation as this discussion may help to pave the way for a better treatment in future studies.

The motivation for the model proposed by Jayasinghe et al. seems to be a somewhat philosophical view that CKDu is a disease that cannot be linked to dominant, easily characterizable simple causes. Thus the authors claim to reject the “reductionist” approach arguing that it fails to capture certain emergent modes found in complex systems (CS). It is not clear if Jayasingha et al. believe that ALL the causative factors (CFs), even if weak, indicated in their organigram (see Fig. 1) model of the organism and the environment as a complex interacting system (MCS) are considered to be necessary and sufficient to cause CKDu. No clarity is afforded as to whether certain CFs, or all displayed act together and become synergistic. Furthermore, it is surprising to find that no antagonistic factors are included in their MCS. Thus, the presence of concentrations of Zn$^{++}$ ions that significantly exceed the concentration of Cd$^{++}$ ions possibly present in the dietary intake is known to largely nullify the usual nephrotoxicity of cadmium [27, 51, 26]. This antagonistic factor is not included,
and constitute one example of a serious lacuna found in the MCS of Jayasinghe et al.

In chapter 9, section 3 of the Ref. [32] we have discussed how standard methods of scientific investigation recover emergent modes quite easily. Very often, the emergent mode can be identified without a complicated systems analysis as many feed-back loops can be easily identified. In the case of chronic kidney disease (CKD), a trivial emergent mode is seen in the feedback loop connecting the decreasing renal mass and increasing glomerular and tubular damage. This is embodied in the “hockey-stick shaped” emergent characteristic of the plots displayed in the toxico-kinetics of chronic kidney disease. Thus the toxic effects are very weak and almost linear as a function of time in the early stages of the disease, but sharply rise beyond stage two of CKD and most probably in CKDu as well. This is due to feed-back effects coming into play. While one may identify this particular feed-back loop in Fig. 1 which connect the box labeled “low-renal mass” (LRM) to the box labeled “rapid decline in GFR” (RDGFR) and back to “low-renal mass”, it does not provide a means to construct the corresponding toxico-kinetic equations or determine the emergent modes.

Two other trivial feedback loops are found in the MCS figure of Jayasinghe et al. One of them is the upper loop going from low birth weight (LBW) to CKDu and then, through “poverty” and “malnutrition” to LBW of a new born. So the time scale of this loop is of the order of a trans-generational time $\tau_g$. A similar lower loop goes through the box labeled “subclinical effects during pregnancy”. This also has a trans-generational timescale. However both these loops, as well as the renal-mass loop suggest that within time scales $\tau < \tau_g$ the mother is also very weakened, and vulnerable to CKDu or other diseases, and hence may not live long enough to give progeny. Hence these two loops
become unimportant. Further more, the very structure of the complex system proposed by Jayasinghe et al. leads us to the view that women are more likely to contract CKDu. In fact, most field studies [3] suggest that men are more likely to contract CKDu than women although other views exist [14].

We may also note that no other emergent modes except the ones enumerated here are likely to arise in the model of Jayasinghe et al. This is discussed further in sec. 4. The authors themselves have not indicated any emergent modes while hinting that emergent modes may arise. Presumably, the causal factors associates with the five arrows that direct to the loop connecting LRM to RDGFR cause the rapid decline in renal function. But how this happens, and if they are even relevant, have to be assessed elsewhere. In act, the only experimentally established synergies for Sri Lankan CKDu are those established by Wasana et al. [11] in research carried out by the team of Banadara et al.

For more complex situations, a particularly useful approach is afforded by artificial intelligence (AI) and neural network-type models. They enable one to “train” a neural network and improve on its predictive quality as more and more new data are fed into it. A short introduction to such neural networks in a general context may be found in Chapter 2, Sec. 2.5 of Ref. [32]. The type of field data needed for such studies is not currently available for CKDu.

Another short-coming of the Jayasinghe model is that it does not take local effects into account. Its components can can apply to any part of the country, except for the box labeled “fluoride, high ionicity and hard water”. That only applies regolith-aquifer fed areas in the country. CKDu has been found in those areas, previously jungle, after they were settled under the Mahaweli irrigation scheme in the 1970s. Furthermore, no CKDu is found in all the areas where that box is not applicable, even though all other boxes, e.g., poverty, malnutrition, contamination, low birth weight etc., are all found in other parts of the country where manual workers labour under the tropical sun. Interestingly, animals that consume agricultural water (in paddy fields, canals) are subject to all the causative factors in the Jayasinghe-Zhu model, except high-ionicity well-water containing F− and Mg+++, and they do not contract CKDu.

"Multifactorial" models. – Given that various investigators of CKDu have proposed many possible causes, some authors have suggested that the etiology of the disease is ‘multifactorial’ [33]. Such proposals are less ambitious than the attempt to set up a dynamical multifactorial model [1]. However, the mere fact that various authors have proposed various (different) causes does not by itself establish a multifactorial etiology for a disease. The model given by Wimalawansa is currently lacking in any detail and use categories like “Environment”, “unidentified toxins”, etc., and hence it is not too different from saying that the etiology is unknown.

In our view, the evidence available so far suggest that CKDu is caused by a single aetiological factor, namely, the simultaneous occurrence of fluoride and magnesium ions (present as a component of hardness) in drinking water drawn from regolith aquifers.

In effect, the MCF presented by Jayasinghe et al. can be regarded as an
improvement over previously presented “multifactorial” models. While there are many factors that cause CKD or CKDu in different situations, and hence require different strategies for their prevention, the claim of multifactorial origin should strictly mean that we know, and can identify, several factors that definitely contribute to the origin of the diseases in that those causative factors are necessary and sufficient for causing CKDu. When such information is not available, including a variety of factors in an organigram or changing the name to ‘multifactorial origin’, or to “agricultural nephropathy” can be quite misleading. That the complex-system model can be easily misused is best explained using a counter-example.

3. A counter-example based on the Jayasinghe et al. MCS

In this section we reuse the causative pathway model for CKDu given by Jayasinghe et al., and slightly modify it to apply to a hypothetical attempt to understand the etiology of malaria (or lung cancer) imagining a time where their origins in the mosquito vector, (or tobacco smoking) were not understood. The modified flow diagram is given in Fig. 2 for malaria. Those boxes which have been modified from the CKDu model of Jayasinghe et al. are marked with thicker lines. A similar modification can be done appropriately for lung cancer to propose that an emergent multifactorial mechanism, and not tobacco smoking, is the cause of lung cancer!

In effect, using such a model we can argue that malaria is an emergent property of the environmental factors associated with various types of air pollution and “bad air”. Prior to the recognition that malaria was spread (or ‘caused’
in popular parlance) by mosquitoes, the Italian name “mala-aria” revealed the common belief about the etiology of the disease. This counter example illustrates the danger of using such ‘multi-factorial’ models as “explanations” inclusive of ‘lots of small causes working together’ to ‘explain’ the etiology of a disease.

**Conditions for several causative factors to add together.** – Causative factors can add together and act synergistically when suitable microscopic mechanisms exist. Additionally, one process may be able to provide energy to push another process forward, and augment the process. However, if the number of weak processes is large, then a form of the central-limit theorem comes into play, and instead of synergistic action, we end up with processes that merely contribute to ‘white noise’ while only the effect of the dominant factor will appear, distributed as a Gaussian. A more formal discussion of emergent modes is given in the following section.

4. Application of a formal theory of emergent modes to the current model.

In the following we apply standard coupled-mode theory to discuss emergent modes in the problem of the response of an organism to environmental causes, within a complex system containing at least one feedback loop. As already discussed, there is just a single feed-back loop of any relevance in Fig. 1. This is the loop connecting “low-renal mass” to “rapid decline of GFR” and back. There are five processes that are depicted in Fig. 1 as contributing to it, via five arrows. Identifying each arrow by the box directly connected to it, these are (1) dehydration, (2) heat stress, (3) other causes of injury, (4) contaminants, and (5) fluoride and ionicity. Of these, in our opinion, the first four have negligible weight and are irrelevant. We assume that the variables have been orthogonalized in the standard way by an eigenvector analysis, or factor-group analysis. For simplicity of discussion, let us assume that the orthogonalization step did not mix the causative agents strongly, so that the original choice of causative agents are already effectively independent causative factors. Let us assume that they are all included with weights $w_i, i = 1, 5$. Their inputs into the feedback loop are described by the vectors $X_i(t)$ at the time instant $t$. That is, each causative factor is associated with its input vector $X_i$. The effect of each causative factor on a chosen kidney function characteristic (e.g., GFR) is denoted by $F(t)$.

$F(t)$ changes by an amount $\Delta_i F(t)$ under the $i$-th causative factor. Then, if there is no feed-back loop action, we can formally write the response of the renal system to the $i$-the environment factor by the relation

$$\Delta_i F(t) = \xi_0^i(t) X_i(t)$$  \hspace{1cm} (1)

Here $\xi_0^i$ is the “zeroth order” response of the renal system to the $i$-th environmental causative factor. As we are dealing with “chronic” effects, i.e., effects
that act over a length of time, unlike acute toxicity, these effects are weak but cumulative. Hence the use of a linear-response form is probably well justified. As no feedback effects or interactions between causative agents are included at this stage, we call \( \xi^0 \) the zeroth-order response. This can be determined experimentally by monitoring the change in renal function under the action of the given environmental factor. The above equation is the effect of just the \( i \)-th causative agent. Thus the total effect of all five causative factors acting on the renal system with no feedback effects, or synergistic or antagonistic effects can be written as

\[
\Delta F(t) = \sum_i w_i \xi^0_i(t) X_i(t)
\]

(2)

To proceed further, we assume that each causative agent acts on the renal system via an interaction factor \( V_i \) associated with the time scales \( \tau_i \). Furthermore, we transform the variables \((X_i, t)\) to work in the Fourier space of \((\vec{K}_i, \omega)\) where \( \omega \) is a frequency. Then the time scales \( \tau_i \) are replaced by their corresponding frequencies \( \omega_i \). Then the total response \( \xi_T(\omega) \) of the renal-GFR feedback loop to all five environmental agents can be written as:

\[
\xi_T(\omega) = \sum_i w_i \frac{\xi^0_i(\vec{K}_i, \omega)}{1 - V_i(\vec{K}_i, \omega) \xi^0_i(\vec{K}_i, \omega)}
\]

(3)

In the approximation where the effect of each environmental factor is characterized only by the time-scale \( \tau_i \) that it sets on the life of the renal system, the above equation can be simplified and written in the form:

\[
\xi_T(\omega) = \sum_i w_i \omega_i^2 / (\omega^2 - \omega_i^2)
\]

(4)

Note that each term has a pole at \( \omega = \omega_i \) so that the lifetime of the renal system under the \( i \)-th environmental insult is \( \tau_i \). At this level of analysis, the environmental factors are acting additively on the renal-mass-GFR loop without any synergistic or antagonistic effects included. To include such effects, for simplicity, let us consider just two environmental agents to become synergistic, say the pair \( i = 1 \) and \( 2 \), and let their interaction be denoted by \( V_{12}(\vec{K}, \omega) \). If there are no interactions between a given pair, the corresponding \( V_{ij} \) is zero. These can be regarded as toxico-kinetic terms that have to be determined from experiment or from physico-chemical energy considerations [7], or possibly from a fundamental model of biochemical processes. Here we simply assume it to be available data characterizing the complex system. Then the synergistic or antagonistic effect changes the first two terms of the equation (4) and gives the form

\[
\xi_T(\omega) = \frac{w_1 \xi^0_1(\omega) + w_2 \xi^0_2(\omega)}{\{1 - V_1 \xi^0_1\} \{1 - V_2 \xi^0_2\} - \xi^0_1 |V_{12}|^2 \xi^0_2} + i > 2 \text{ terms}.
\]

(5)

The new denominator no longer has poles at \( \omega_1 \) or \( \omega_2 \). Instead, new poles are given by the roots of the equation

\[
\{1 - V_1 \xi^0_1\} \{1 - V_2 \xi^0_2\} - \xi^0_1 |V_{12}|^2 \xi^0_2 = 0.
\]

(6)
These roots define the new, or “emergent” modes resulting from the synergistic or antagonistic interactions, and give new time scales \( \tilde{\tau}_1 \) and \( \tilde{\tau}_2 \). If the interaction is antagonistic, the time scales \( \tau_1, \tau_2 \) corresponding to the original poles \( \omega_1, \omega_2 \) get lengthened to such an extent that renal damage will not occur within the patient’s lifetime. On the other hand, if the causative factors act synergistically, then the lifetimes \( \tau_1, \tau_2 \) will be shortened significantly and will also shorten the lifetime of the patient.

4.1. Can many below-threshold effects contribute to become a significant emergent cause?

The zeroth-order time scales \( \tau_i \) or their corresponding frequency values \( \omega_i \) of below-threshold are such that their effect would be felt only if a human being lived to a thousand years or so. So, even if a hundred of them joined together to give new renormalized time scales \( \tilde{\tau}_i \), they will still be too far out to have any effect within the lifetime of a patient. In fact, the logic behind setting thresholds of chronic toxicity is precisely that no toxicity was observed and not expected to be observed under long term monitoring. It is always usually the case that besides the many below-threshold effects, there are usually a few dominant effects that carry a high statistical weight based on the available evidence.

In Fig.1 the statistical weights \( w_i \) seem to be negligible except for the fifth case, imposing the reductionist picture by the weight of evidence. That is, the action of consuming fluoride and magnesium ions found in wells supplied by regolith aquifers prevalent in the endemic regions is by far the most significant causative environmental factor for CKDu.

5. Conclusion

The construction of models of complex systems, as well as the mechanisms of origin of emergent modes is well understood and requires much more stringent and accurate data than are needed for models that are derived from a reductionist approach where the number of variables is strictly controlled by designing suitable experiments. Complex systems (see chapter 2, Ref. [32]) can be built up with confidence only when experimental information is available on a large number of reductions of the more complete system. This is in fact a major problem in environmental studies. These limitations of modeling complex systems make it extremely easy to obtain false conclusions from ‘complex-system’ models.

6. Funding

This research did not receive any specific grants or financial support in any form from funding agencies in the public, commercial, or not-for-profit sectors.
7. Declaration of competing interests

The author has no known competing financial, commercial or personal interest in the work reported here.

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