filovirus research: the need for an integrated approach in time and space

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THREE THEMES THAT NEED TO COME OUT IN THE PAPER: The episodic appearance of Ebola virus (EBOV) and Marburg virus (MARV) across central Africa over the last 15 years not only underscores the importance of filoviruses as uniquely virulent agents to both human and wildlife communities but also implies a very complex transmission scenario that must be understood if we are to prevent or mitigate filovirus outbreaks in the future. Efforts of a global network of scientists and healthcare workers have expanded our knowledge of filoviruses to meet the growing threat of Ebola and Marburg hemorrhagic fevers in Africa.

In recent decades, several newly emerging diseases have resulted in major threats to both affected communities and global public health. Viruses from wildlife hosts in particular, have exhibited a capability for cross-species transmission (CST), and have caused high-impact diseases in humans such as Ebola and Marburg hemorrhagic fevers, Nipah and severe acute respiratory syndrome (SARS). It has been estimated that about 60.3% (Jones et al. 2008) of human infectious diseases are of animal origin (zoonoses) and even some important viral diseases that are traditionally considered of human origin, for example measles and smallpox, may very well have their prehistoric origins in wildlife (Wolfe et al. 2007). It maybe logical and prudent therefore, to anticipate that there are other, new filoviruses out there that will cross into humans at some point in time. If we anticipate that these will happen and wish to be prepared for and mitigate this potential, then an understanding of filoviruses as a biologic system in the environment will be essential to that process. We will need to know how the ecological dynamic of CST interacts with a 'new' virus's evolutionary factors to overcome environmental, demographic and host-specific barriers to transmission and infectivity to humans. First, in the specific case of filoviruses (Ebola and Marburg), there is still limited knowledge about what is the true animal reservoir. Recent studies do finger frugivorous bats as the likeliest suspects (Leroy et al. 2005, Swanepoel, et al. 2007, Towner et al. 2007, Pourrut et al. 2009). But, uncertainty remains. Knowing the reservoir(s) is critical if we are going to narrow our research to those ecosystems most likely to inform "smart surveillance". That is the targeting of those regions believed to be high-risk hotspots for filoviruses emergence and human risk (Pinzon et al. 2004). Finally, to grasp the full complexity of a successful filovirus CST, one needs to consider

many other factors including the type and intensity of reservoir, intermediate and final host contacts. These are affected by social, behavioral, seasonality, and ecological traits. To deal with the emergence of filoviruses in its entirety then, we need to study the whole dynamic of filovirus transmission and emergence as an integrated physical and biological system, not piecemeal. This assumes that emergence is a natural system, and it possesses the essential characteristics of a complex adaptive system (CAS, Holland 1995). These characteristics include: 1) **heterogeneity** of interacting components (species, agents, vectors, hosts, humans, environment and climate), which provides variability through 2) **nonlinear** interactions among those components. The interactions among the parts determine and reinforce a 3) **self-organizing hierarchical** structure. CAS defines the rules that govern which plants and animals can be expected in an environment, and how they have adapted for successfully living there. By using the deductive perspective of CAS (Levin 1999), together with the hierarchical organization as a starting point, we should be able to abstract out the filoviruses' potential transmission enablers and explore through simplified models the properties that should be present in their filovirus transmission and emergence into humans. For example, we know that some forms of contact between donor and recipient host is a precondition for virus transfer. It is therefore negatively affected by a hierarchical structure that separates the donor and recipient - the barriers of geography, ecology and behavior, etc. In theory, factors that disrupt the geographical distribution of host species (e.g. wildlife trade and migration due to climatic and environmental shifts like drought or habitat destruction) or that decrease behavioral separation (e.g. bush meat hunting) tend to promote new avenues of interaction between reservoirs and hosts, opportunities for virus sharing and the emergence of infections in new host species. In the case of filoviruses, these barrier disruptions can explain the spatial pattern of sporadic or occasional human

outbreaks. In addition, the seasonality of climate and the corresponding uneven temporal distribution of resources needed for existence, place hardships on both wildlife and humans. These also tend to decrease barriers to transmission, but in a more cyclic pattern. Thus, the CAS for filoviruses in general, may comprise both an eco-climatic set of conditions that trend on a given temporal scale, as well as a geographic, behavioral set of factors that trend on a totally distinct scale. Seasonality is tracked by eco-climatic information, which in turn is used to characterize places by their patterns of temperature and precipitation. This tracking allows us to estimate the distribution and patterns of vegetation growth, which in turn, allows us to construct schemes for relating vegetation to the on-the-ground effects of climate. We postulate that one of those effects is disease emergence.

Stepping back for a moment, science as a disciplined thought process, begins from observation and interpretation. It then seeks explanation and mechanisms (Levin 1999). It comes up with a strategic concept for examining apparently unpredictable natural events by averaging its observations over time and space. It's a starting point; but that is obviously not enough. The average needs to also be applied in a proper scale to relate its findings in a meaningful way. For example, natural occurrences tend to come into focus on certain scales (temporal/spatial), and not on others. Thus, scale matters when we try to relate disease emergence characteristics and environmental conditions. Different degrees of aggregation show different views of system dynamics. On broad spatial scales and long temporal scales, ecological systems in their entirety exhibit well-established patterns upon which one can derive reliable generalizations (relevant to modeling and prediction). Variation among observations, however, occur. They may be apparent events, and non-consequential to the dynamic, or expressions of impactful trends expressed at different or smaller scales, and periodically becoming noticed because they

individually cross the magnitude barrier of a larger scale that is in play, or because they converge and augment the expression of the larger scale. So where does this lead to in filovirus emergence? What do we know about the relationship of these viruses to various scales? How does 'scale' relate to their CAS? Can we use scale or CAS to design an appropriate tool for conducting surveillance for filovirus emergence?

Marburg virus (MARV) and Ebola viruses (EBOV) comprise the known main etiologic agents in central Africa that cause filovirus associated severe hemorrhagic fevers (HF in both human and non-human primates (Sanchez et al. 2007). The high pathogenicity of these 'prototypic' filoviruses has been apparent since the discovery of MARV HF among vaccine plant workers in (Marburg) Germany and the former Yugoslavia in 1967 (Kissling et al. 1968). Interestingly, almost 10 years later, in 1976, a second filovirus, and the first that became apparent in a natural setting, emerged in two nearly simultaneous outbreaks about 800 km apart in southern Sudan and Zaire (present Democratic Republic of Congo, DRC) and led to the discovery of two EBOV subtypes, Sudan Ebola virus (SEBOV) and Zaire Ebola virus (ZEBOV) (Smith 1978, Johnson 1978). The ZEBOV epicenter was in Yambuku, a rural village with the Ebola river running through it in northern DRC. The mortality rate for ZEBOV was about 80% and 50% for SEBOV. In 1989, a third strain/subtype of EBOV, named Reston Ebola virus (REBOV) was identified in infected macaques in a quarantine facility in Reston, Virginia, USA; the monkeys being imported from the Philippines (Jahrling et al. 1990). REBOV is lethal to monkeys but appears to be non-pathogenic in humans. EBOV HF was not reported again until the end of 1994, when three outbreaks started almost simultaneously. In November of that year, ethnologists studying chimpanzees in the Tai National Park, Côted'Ivoire, found dead chimpanzees and noticed the

absence of others. A female researcher became infected during the necropsy of one of the dead chimpanzees, and a fourth novel strain of EBOV, the Cote d'Ivoire (CIEBOV), was isolated from her blood.(Formenty et al. 1999). Then, that December, multiple human ZEBOV HF cases were reported in gold panning camps in Gabon, and a large human outbreak began in the Kikwit District in DRC. The Kikwit outbreak resembled the 1976 outbreaks in that secondary transmission of the virus occurred through close personal contact between family members and among hospital workers. A fifth EBOV subtype, Bundibugyo Ebola virus (BEBOV), was identified in November 2007 from cases in an outbreak in Bundibugyo district, Uganda. Unlike the other EBOV outbreaks, the new strain had a case fatality rate of 25% (Towner et al. 2008). Interestingly, since the EBOV outbreaks of the mid 1990's, there have been sporadic reports of human and non-human primate cases. (Walsh et al. 2003, Pourrut et al. 2005, Towner et al. 2008, Cardenas 2010). Overall, the reported outbreaks have included: ZEBOV - one isolated case in South Africa (1996, imported from Gabon), and ten outbreaks with high near-uniform lethality of 80% (in DRC: 1995, 2007, 2008; in Gabon (1994/1995, 1996, 1997, 2001/2002); and in the Republic of Congo (2001, 2003, 2005). There have been two SEBOV outbreaks - one in Uganda (2000/2001) and one in Sudan (2004). Both had a case fatality rate near 50%. There has also been one isolated human case of CIEBOV in Ivory Coast (1994), and one reported BEBOV outbreak in Uganda (2007/2008). MARV has also proven itself to be a recurring threat in central Africa with its severe morbidity and high fatality rate in the recent outbreaks in DRC (1998-1999) and in Angola (2004-2005).

This diversity of the magnitude and location of these EBOV and MARV outbreaks, but their very similar presentation and severity of disease suggests that while the various filoviruses have similar pathogenic characteristics and host tropism and possibly human-exposure dynamics,

something in their pathway to outbreak emergence is causing variation in their observed temporal cycles and spatial patterns that are not immediately evident from a linear analysis. Attempts to unravel the known and relevant details of filoviruses emergence has caused us to start with inferences from circumstantial evidence and correlations; not very satisfying scientifically for modeling/prediction, but inference from such information does provide an adequate place to begin formulating hypotheses. But then these must be probed for verification or rejection. Using the CAS rubric and approaching the interpretation of our observations through the use of multiple scales, we may be able to tease apart the biologic, environmental and temporal connections that describe a plausible filovirus emergence model. We can then use the hypothesized model to probe for scientifically verifiable explanations and understanding of the complex pattern we are seeing, and begin to understand how filoviruses in general emerge. This probing will require the incorporation of recent advances in a number of disciplines, relevant for modeling and prediction making, collaborative initiatives between virology, veterinary, human medicine, climate and ecology.

So, as a starting point, we know that during known outbreaks, the spread of Ebola virus among gorillas and chimpanzees in the border region between Gabon and the Republic of the Congo (RC) has caused both a high number of deaths among these primates and a series of human cases with histories of contact with infected animals in the jungle (Walsh et al. 2003, Rouquet et al. 2005). More specifically, strong evidence obtained during the ZEBOV HF epidemics in Gabon, indicates that hunters acquired infection from scavenging gorilla, chimpanzee and duiker carcasses (Walsh et al. 2003, Leroy et al. 2004, Rouquet et al. 2005, Lahm et al. 2007). Leroy et al. (2004) found that great apes can be infected with ZEBOV under different ecological conditions through independent transmissions events. This suggests that there is a wide

distribution range for these viruses. We also know that because of their high case fatality rates, great apes are presumed to be dead end hosts; and thus when combined with the discordance of filovirus event locations and the great apes' natural geographic distributions, apes are unlikely to serve as the viruses' reservoir host. Current evidence does suggest that because of virus isolation studies and the known geographic range of some species of frugivorous bats, there is a very strong case for these animals to be the filoviruses' natural reservoir (Leroy et al. 2005, Swanepoel, et al. 2007, Towner et al. 2007, Pourrut et al. 2009).

From what we know of these bats, they appear to bear their young in a synchronous timing with wet seasons, when food (fruits) is most abundant in their habitats. We also know that this is a shared food with great apes. Therefore, an assumption has been made that the behavior around and the process of birthing can be the mechanism for filovirus shedding, and hence the plausible biologic source of a primate's increased exposure to virus. Furthermore, recent analyses of known environmental and climatic factors associated with EBOV activity support this assumption. In the tropical forest areas of Gabon and DRC (Tucker et al., 2002; Peterson et al., 2004; Pinzon et al., 2004) at approximately 2-4 months after the onset of markedly drier environmental conditions, [1] during the longer and first of two yearly wet seasons, (Pinzon et al., 2004) multiple incidents of ZEBOV have been reported.

Given what we know to date about filovirus emergence, and using the thought process above, the NASA-Goddard Space Flight Center (GSFC) team has attempted to model proxy indicators of EBOV HF risk, and characterize areas endemic to this infectious disease. To start, NDVI was

[1] Lower than 1.5 standard deviations from the mean NDVI value (Pinzon et al. 2004).

used to characterize the vegetation type(s) associated with EBOV HF outbreaks and the temporal and spatial vegetation patterns in the wet and dry season during those events. Landsat data has told us that all reported Ebola hemorrhagic fever outbreaks occur in either tropical moist forest or gallery tropical forest in a savanna matrix (Tucker et al. 2002). The information gained from that categorization then enabled us to use extraction methods, such as singular value decomposition (SVD) to identify specific environmental features (or constellation of features) associated with outbreak sites (Figure 1 adapted from Pinzon et al. 2004). This restricted our eco-climatic analysis to only conducive tropical moist forest or gallery tropical forest areas in Africa.

The main result of this first step has been the identification of Gabon-RC region (Figure 2) as an important epicenter of ZEBOV transmission in Africa (Pinzon *et al.* 2004). A first step towards "smart surveillance" - more targeted detection and analysis of what is causing filovirus emergence in theses specific areas (Figure 3)[2].

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[2] Riverine forest can be detected through classification of satellite imaging (DEM, NDVI, temp), and one can track their wet/dry conditions to predict increase of contact assuming that that determines high risk – in other words – environmental conditions affect population dynamics, but more importantly affects behavior – triggering (possibly violent) contact when food is scarce. So in this case, one can develop an eco-climate-driven early warning system for filovirus by monitoring dry conditions that predict (indirectly) increase contact (risk) with pathogen.
If we assume that bats are the link to follow for modeling and prediction, what is known about the ecology and diet of the 3 frugivorous bat species is:

1) They are widely distributed in equatorial Africa and found in riverine forests at elevations less than 1800 meters (where EBOV outbreaks have been reported).
2) Figs are their preferable food, but they also eat mangos and bananas (similar to great apes). According to Langevin (1990) while male bats may forage long distances (15km) to locate good quality food, female bats rely on established feeding routes that offer a constant supply of lower quality food.

This leads to the question of why the difference between dry seasons and animal behavior; transmission opportunity between those two dry seasons in a year, and across different years. Are the biology or behavior of the reservoirs or the eco-climate interactions or a combination of these two drivers of the observed temporal scales causing both the larger 20 year cycle of outbreaks and a smaller cycle of sporadic cases?

CST has been related to changes in fruit availability and dietary composition during environmental hardship, but is virulence a domain only of the reservoir or is there the seasonal variation in the fruit attractant, its nutritional quality that changes the exposure level or susceptibility of the primate to infection by the virus? These questions need to be addressed by future research into the reservoir hosts and into the infected animals.

What is also intriguing, and a question that is more germane to our analysis here is, if the reservoir hosts are in fact 'similar' in filovirus transmission capability, then do all outbreaks, large ones and small, follow a similar temporal pattern driven primarily by host factors in association with eco-climatic trends and conditions? The difficulty with this explanation resides in the different ecologic and temporal scales involved. If we step back a moment and ask if there is a common thread that runs through all this biotic complexity, one wonders if there isn't an underlying abiotic or environmental condition or trend, or convergence of conditions and trends, which better explains what has been observed to date –filovirus outbreaks vs sporadic cases. This variation suggests more than one 'environmental temporal frequency'. Could the favorable conditions for outbreaks occur at different temporal scales, at different frequencies, from local through regional to multi-regional variability. Environmental processes occurring at the local scale could affect the rates of virus exposure and transmission, including human and animal behavior, e.g. hunting patterns -- human exposure to the risk also increases under these conditions since bush meat preferences of village-hunters change to a wider array of animals (Walsh et al. 2003, Leroy et al. 2004, Rouquet et al. 2005, Lahm et al. 2007). Environmental processes (the same or other) can affect regional scale processes as habitat conditions, e.g. vegetation, precipitation, and landscape patterns. Multiregional effects could

also occur when climatic signals, e.g. El Niño Southern Oscillation (ENSO), North Atlantic Oscillation (NAO) indices, influence regional cycles and patterns[3]. These processes influence the risk of contact with the pathogen and happen at different (spatial and temporal) scales.

Recasting our hypothesis, seasonal forecasts of filovirus epidemics based on climate and vegetation patterns can be available for specific regions at different levels of accuracy and their forecast lead-times vary according to the different scales of the climate and vegetation parameters. Implicit in this assumption are the essential characteristics of the CAS system: heterogeneity, nonlinearity and hierarchical structure. What we proposed is a hierarchical approach that uses nonlinear methods, the empirical mode decomposition (EMD)[4], to explore the observable interactions among the integrated physical and biological systems involved in filovirus epidemics at different (temporal) scales (Figure 4). To start, we decompose the NAO signal and Gabon-RC NDVI-based EBOV HF risk into their different intrinsic EMD modes of oscillation. Figure 5 reveals that a 3-year oscillation component of the NDVI-derived EBOV HF risk swings 15-20 months lag with a 3-years NAO component that rides over a 10-years mode that at the same time appears to be modulated by a 20-years cycle. These components could

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[3] The NAO index is typically measured through variations in the normal pattern of lower atmospheric pressure over Iceland and higher pressure near the Azores and the Iberian Peninsula (Jones et al. 1997, Hurrel 1995). The ENSO has two cycles: strong negative (El Niño event) and strong positive (La Niña event). Several indices have been developed as indicators of the onset of ENSO cycles (Glantz 2001), such as sea-level pressure the so called Southern Oscillation index (SOI), along with changes in Pacific sea surface temperature (SST). SOI is measured by the difference in pressure between the opposite ends of the oscillation's seesaw, Tahiti and Darwin. Wolter and Timlin (1998) combined SOI and SST along with four more observed variables over the Tropical Pacific to create a more robust index, Multivariate ENSO index (MEI).

[4] The traditional method to identify noise, trends and oscillations in a dataset is through linear approaches, i.e. Fourier analysis-based filtering in frequency space. The Fourier method is not applicable here, although it might be useful for many other applications. Fundamentally, natural variations (CAS systems, in general) involved nonlinear processes, thereby violating the underlying assumptions of stationarity and linearity of Fourier Analysis. As an alternative, we employ the newly developed adaptive time domain Empirical Mode Decomposition (EMD) as method of filtering. EMD is designed to seek the different intrinsic modes of oscillation in any data, based on the principle of local scale separation, without requiring any predetermined basis functions. EMD has been described in detail in previous publications (Huang et al. 1998, Wu and Huang 2009, Huang et al. 2009).

be part of the mechanism for the observed epidemic 20-years cycles, perhaps explaining why epidemics have been so unpredictable in their timing and location. Thereby, analyzing these compatible observable swings, we could derive physical mechanisms and predict inter-annual variability of temperature, precipitation and vegetation patterns associated with filovirus epidemics with lead-time of several seasons. Spatial uncertainty (scaled dependent) can be reduced by analyzing shorter temporal cycles at higher spatial resolutions (Figure 4). This will require "ground truth" data (epidemiological, animal and vector data collected from active or passive surveillance, or field surveys) to be integrated into modeling as (local) explanatory mechanisms as well as validation tools (landscape epidemiology) and achieve smaller quantitative uncertainty ranges while improving robustness and accuracy in the risk prediction. Making the scientific understanding of space imaging and prediction of infectious diseases widely accessible raises particular challenges by itself since it involves accumulated uncertainty in its core – uncertainty interacting with risk assessment which depends on the confidence on the level of understanding of the relevant science, the nature of associated (local) risk factors, and on the types of decisions that the risk assessment might influence. Nevertheless, once the model template is organized (Figure 4), a more precise context for decision making of exploring scenario assumptions could be attainable in risk management. The concept of risk adopted in the prediction is the likelihood that some event will occur; when it is used on decision making, it translates into the magnitude of the consequences of that event when specific scenario assumptions are considered. In other words, there is a need for a versatile way to report this scientific and technological information and foster the dialogue between scientists and non-specialists (decision makers, citizens, consumers) regarding risks, decision costs and decision-tools improvements.

In summary, the monitoring and surveillance of climate factors based on the association of disease inter-annual cycles (local interactions) to climate variables at the regional and

multiregional scales could be the most easily implemented tools for best management practices in control and prevention of filoviruses. Moreover, monitoring wildlife population dynamics along with environmental factors have the potential of acting as sentinels of developing infection threats and could help in the investigation of the natural reservoir of EBOV and MARV. Such studies would allow a better understanding of some of the CST mechanisms of filoviruses, perhaps shedding light on the natural history of filovirus, and, it may also serve as a future testing ground for educating local populations, improving case detection, and developing a rapid, timely, and effective outbreak response all under a coordinating rubric of the World Health Organization.

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FIGURES

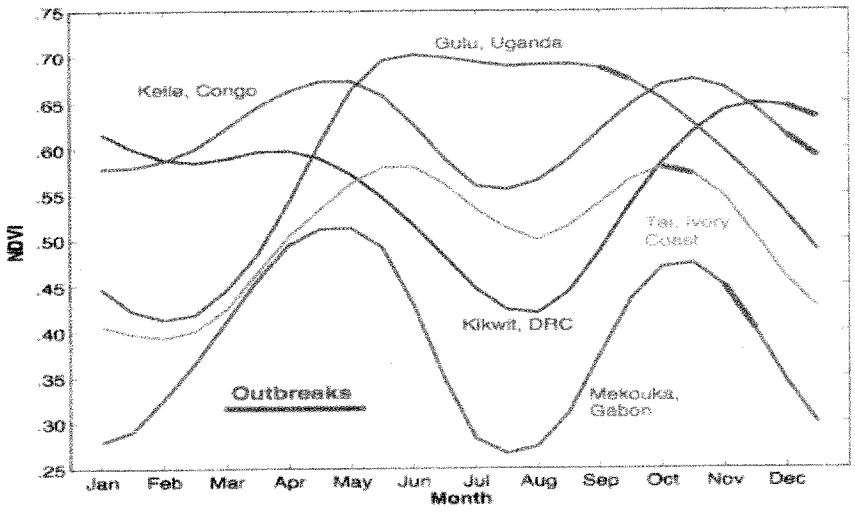

Figure 1. Time series behavior of the NDVI data from the documented outbreak sites of EBOV HF. Note that all outbreaks occur toward the middle of the second dry season. Adapted from Pinzon et al 2004.

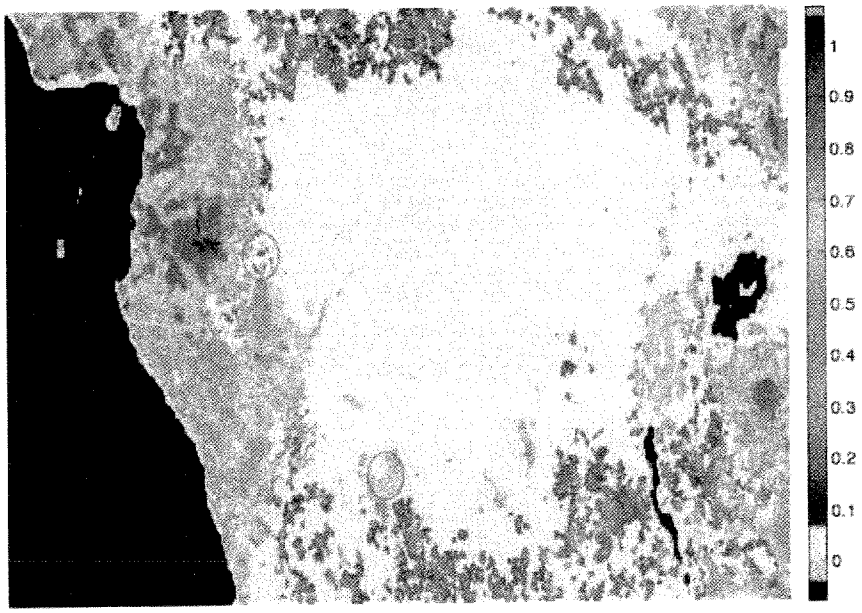

Figure 2. Regions where EBOV HF is found endemic. The recent ZEBOV outbreaks provide groundwork evidence to consider the regions within Gabon and Republic of Congo borders and south DRC as the "Ebola Hot Zone". Adapted from Pinzon et al 2004.

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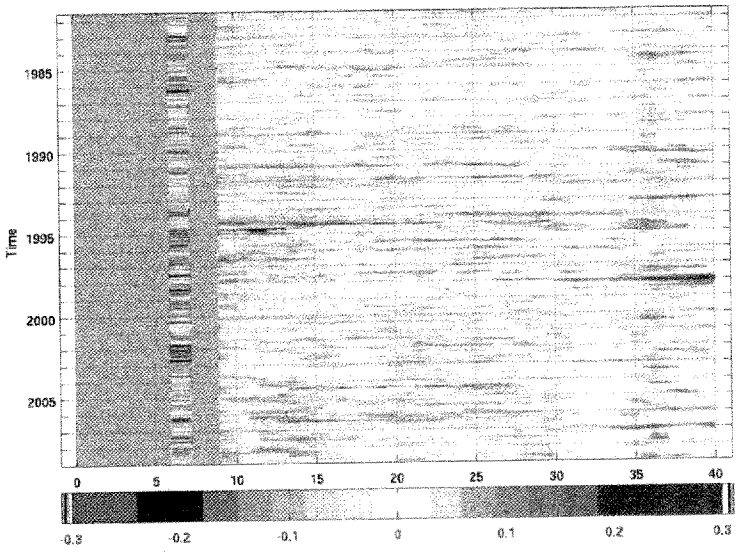

Figure 3. Hovmoller anomaly NDVI image of the "Ebola Hot Zone" (figure 2). Notice the markedly drier environmental conditions in 1991, 1994, 2000-2001 and 2004. EBOV HF was dormant for about 20 years until the end of 1994, when three outbreaks started almost simultaneously.

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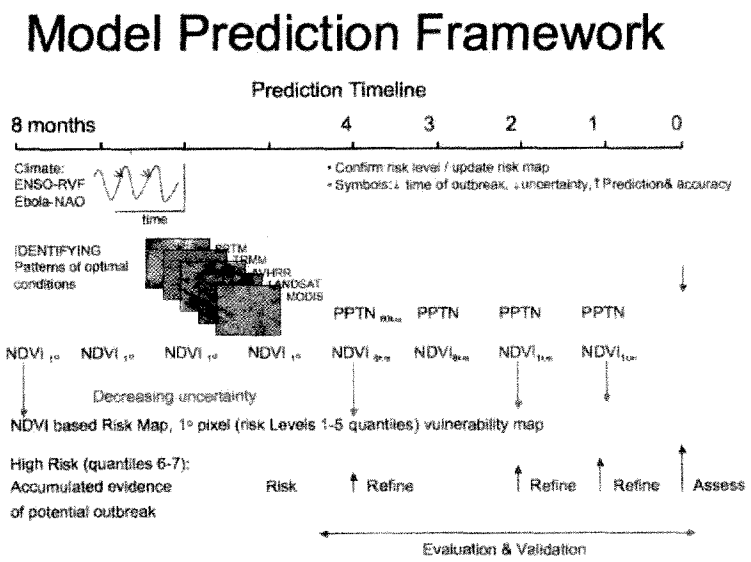

Figure 4. Developing a multi-level risk map with dynamic decreasing uncertainty and increasing temporal and spatial accuracy that reinforce expandability and accessibility.

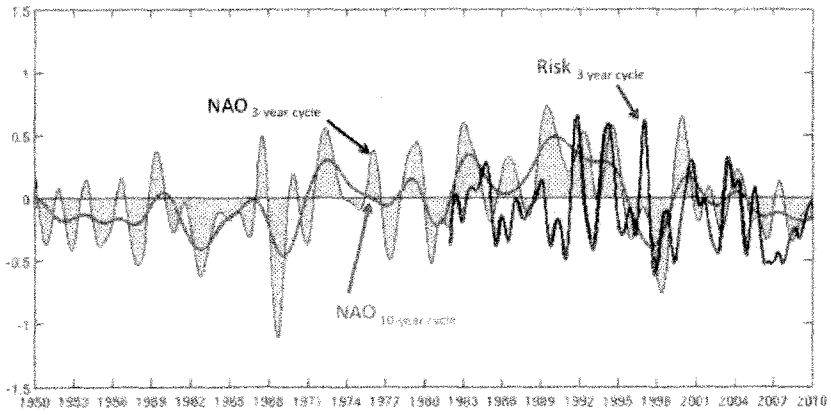

Figure 5. Decomposition of the NAO signal and "Ebola hot-zone" NDVI-based EBOV HF risk into their different intrinsic EMD modes of oscillation. A 3-year oscillation component of the NDVI-derived EBOV HF risk swings in a 15-20 month lag with a 3-year NAO component that rides over a 10-years mode modulated simultaneously by a 20-year cycle.