The Origin and Maintenance of Tuberculosis is Explained by Its Subclinical Course, the Neolithic Revolution Being the Trigger for Its Devastating Deadly Drift

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Research Article

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The origin and maintenance of tuberculosis is explained by its subclinical course, the Neolithic revolution being the trigger for its devastating deadly drift.

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SUMMARY
The origin of *Mycobacterium tuberculosis* infection has recently been dated to the Middle Paleolithic; around 70,000 years before the common era (BCE). At that time *Homo sapiens* was just another primate living in reduced groups in balance with nature, with discrete growth and a very low-density geographic occupation. Therefore, it is difficult to understand the origin of a highly virulent obligate human pathogen. We have designed a new SEIR model (TBSpectr) that considers tuberculosis (TB) clinical spectrum, by including a protection factor (p). The model fits current accepted growth rates for Middle Paleolithic (0.003%/year) and Neolithic (0,1%/year). The data obtained links the origin of *M. tuberculosis* ancient lineages in the Middle Paleolithic to the induction of mild TB forms (Sputum negative), thanks to a high p factor that was further enhanced by evolution towards modern lineages. The poor health status linked to the unequal society existing after the Neolithic revolution increased the incidence of more severe forms of TB (Sputum positive). This data supports the origin of TB as a well-tolerated highly persistent infection which could coevolve towards mutualism, shows the difficulty of eradicating it and highlights the imperative of providing better health conditions to humans to avoid its severity.

1.-INTRODUCTION

The origin of *Mycobacterium tuberculosis* (Mtb) infection in the middle Palaeolithic, 70,000 years before the common era (BCE) as determined by molecular-timing bases[1], creates a great challenge. It is difficult to reconcile how a pathogen with such an extraordinary virulence could coevolve with a host, *Homo sapiens*, which at that time represented a fragile animal species[2,3]. Effectively, tuberculosis (TB) is the major killer of humankind. It has been estimated that it has caused 1,000,000,000 deaths in the last 200 years[4]. This impact appears to be the final phase of a formidable incidence, records of which first started in Europe in the eighteenth century, coinciding with the industrial revolution and the compilation of the first consistent epidemiological records, with mortality incidences in big cities like Stockholm, Hamburg or London, peaking at around 900 deaths/100,000 inhabitants[5]. Even when the origin of this epidemic seemed to be uncertain[6], and although it has been claimed to be the consequence of the sudden emergence of crowded cities[7], there is growing evidence that in reality it had always been amongst us. The reason for the perception of this sudden gap in the European TB incidence may lie in the lack of availability of a precise means of diagnosis until the studies of René Laennec. His work was instrumental in correlating the pathology with the semiology at the beginning of the nineteenth century[8].

Because of the chronic nature of the disease, TB was easily able to remain silently in Europe due to the catastrophic incidence of the ravaging epidemics caused by bubonic plague, cholera, smallpox, malaria or typhus, with their immediate impact; or the chronic diseases causing extraordinary social impact such as leprae or syphilis[9]. In fact, there are several indirect pieces of evidence for the presence of TB covering the gap between the eighteenth century records and the signs of TB demonstrated in archaeological findings (Pott's disease) detected in several Egyptian mummies, and skeletons found in Poland, Spain, Lithuania, Britain and France dated from 4-5th century[10]. In fact, the first description of "phtysis" was by Hippocrates in classical Greece, and the first TB treatment recognized was by the physician Clarissimus Galen, of the Roman Empire[11]. In the Middle Ages there was the illness called "King's evil", which was mainly caused by Mtb, causing cervical lymphadenitis (scrofula), and thought to be healed by the "Royal Touch" a ceremony that started with King Clovis in 496 and lasted until 1712 and Queen Ann[11,12]. King Charles II of England was the champion, as he touched more than 92,000 scrofulous individuals during his 22-year reign (1660-1682)[12].However, it was even earlier, in the sixteenth century, that Girolamo Fracastoro suggested the contagious nature of TB[13]. In 1699 Francis Sylvius was the first to illustrate the pathology of the disease, describing tubercles, cavitation and empyema in the lung, linking it to "consumptive patients". In the same year, it is in the Republic of Lucca that the first official reference is found on the infectious nature of the disease[14].

Due to its condition of obligate pathogen of *Homo sapiens*, Mtb has been evolving with humanity since its origin, and when we examine the historical references it appears to have adapted to all kinds of cultural changes, which have allowed its sustainable evolution despite its incredibly mortal capacity. "Ancient" Mtb lineages appeared by 70,000 BCE at a time when humans were organized in small tribes of hunter gatherers of around 50 individuals living in Africa, with an effective population limited to a million people, who started to expand towards the East in the process known as the second out-of-africa[3,15,16]. This represents a very low population density[17], around 30 people per 100 km^2, which challenges the permanence of many infectious diseases, especially the ones that are human obligate parasites[15]. This low density and sustained "non-growing" condition for hundreds of thousands of years, around 0.003% annually[18], was the consequence of a nomadic style life were child raising had a high cost, for both transportation and breeding, so it is estimated that each woman could only raise one child

every 4 years[19]. Even when child mortality was high (27%) together with infant mortality before 15 years (46%)[20], these people had good quality of life, which resulted in in a life expectancy of around 33 years [19,21] because once they reached the age of 15, 67% of them lived to an age of 45 or older [22].

Interestingly, modern Mtb lineages appeared by 46,000 BCE, at the time of increasing expansion (reaching as far as Japan, Australia and Europe). This lineage is less aggressive, as it is less proinflammatory, but it has a higher capacity to disseminate through aerosols[23], and is the one that finally became predominant in humanity[24]. Mtb expansion was fuelled by the Neolithic revolution and the explosive population growth, of around 0.1% annually, thanks to the progressive change towards sedentary life and faming-based activities, which led to higher birth rates (about one child raised every two years), but with a lower quality of life due to the impact of social inequalities[25,26], harder work duties and less varied nutrition, which caused a reduced life expectancy[21,27].

Several models have been set up to try to understand the origin Mtb infection in the Middle Paleolithic, with such a low-density population. One of the initial ones is based on the hypothesis that the mechanism of infection of Mtb was originally based on a late progression towards active disease (i.e. prolonged latency) of more than one generation, with the possibility that younger and more susceptible individuals became infected[28]. Adapting this criteria, Zheng *et al*. [29] built a model of TB transmission [30,31] using a population of 100 individuals. They concluded that to sustain TB, Mtb would have had to have a high progression to disease of up to 50%, which clearly exceeds the value of 5-10% accepted nowadays [32].

Recently we developed a SEIR model which showed an extraordinary impact of Mtb, which provoked the extinction of the infected groups[23]. This could only be overcome by an unprecedented population increase attributing an annual population growth rate of 1% and 2.6% instead the accepted 0.003% and 0.1% for the Paleolithic and Neolithic[18]. This data had major drawbacks as it required a dramatic rethink of the population growth parameters in Prehistory.

Recent data based on a precise determination of mortality and curation in the natural history of TB in the pre-chemotherapy era oblige us to modify this model. In this work, the authors have been able to better distinguish the prognostic of sputum positive (SP) and sputum negative (SN) patients, as a sign of TB severity[33]. This data shows a dramatic difference between both forms and allows us to better explore the trade-offs that made this coevolution possible. Severe forms (SP) had an annual mortality ratio of 0.389 and self-curation of 0.250, while mild forms, (SN) have values of 0.025 and 0.125 respectively, thus reducing the mortality by 15 times. Taking the TB disease spectrum into account, especially the impact of mild forms is paramount, as it drastically reduces the mortality but maintains the possibility of disseminating the infection, even when at a lower ratio. It is known that people with SP have ten times higher levels of bacilli in their sputum than SN[34]. Thus, we have built a new SEIR model (TBSpectr) in which we distinguish both clinical forms and allocate them according to a protective factor "p" depending on the health status of the host, which determines the induction of one or the other clinical form.

The main objective of our study has been to evaluate the minimum rate of protection needed to induce mild SN TB in order to maintain the consensual annual population growth established in the Paleolithic and Neolithic societies, and also to determine the impact of ancient and modern Mtb lineages.

Our work sustains that Mtb and modern humans could coevolve thanks to the presence of SN lesions, due to the better health status present before the Neolithic Revolution. It was precisely this cultural change that led to the increase of SP forms, even when the predominant Mtb lineages (modern ones) were less virulent. This data supports the extreme conservation of the Mtb virulence factors[35], generated after a long evolutionary process in mycobacterial species, and which had originally stabilized to generate minimal lesions. The establishment of less equal and more stressful societies after the agricultural revolution means that Mtb starts to have a large impact on health. This is in contrast to what was seen during the Paleolithic when it took advantage of persistence in a mutualist relationship by stimulating the innate immune response (i.e. in form of trained immunity). This data highlights the character of TB as a poverty-related disease, and its higher impact on socially depressed sectors of the population. On the other hand, the benign nature of its origin makes Mtb a highly adapted pathogen, which will be difficult to eradicate using the current diagnostic methods.

2.-RESULTS

2.1.-Mtb infection in the Paleolithic was possible thanks to high protective values.

Adjustment of the continuous TBSpectr model (Figure 1) to the currently accepted human population growth rates in the Paleolithic (0.0003%/year) and Neolithic (0.1%/year) (Figure 2) gives us the relation between the natality (λ) and the protective factor (p) that determines the allocation towards SN or SP TB forms. We have considered the demographic parameters for each period of time and Mtb lineage (Table 1). Once obtained we established the natality value (λ) that was able to fit for both Mtb lineages in the Paleolithic (0.032) and Neolithic (0.044) periods, considering the lowest and the highest value, respectively. This has allowed us to determine the value for the protective value (p) corresponding to each Mtb lineage for each cultural period. Thus, the protective values were higher in the Paleolithic (0.488), corresponding to the better health status, which was then increased by the irruption of the modern lineages (0.677), which also corresponds to its lower virulence. In the Neolithic period the clinical forms worsened dramatically according to the protective values, which decreased in both modern and ancient lineages to 0.263 and 0.096, respectively.

We have also looked at the number of children of 15 years old or more (Figure 2B), as the number of fertile individuals available is an interesting factor that contributes to population growth. In this case the difference was not that high between the two periods of time (2.11 vs 2.33)

2.2.-Ancient lineages had to be more virulent in the Paleolithic in order to sustain Mtb infection but had a better recovery rate.

Figure 3 shows the dynamics of the different compartments studied according to the protective factor (p). It is important to note the parabolic evolution vs the exponential decline in SN and SP infectious cases respectively. This indicates the need for the initial Mtb strains, belonging to ancient lineages, to have a higher virulence than the modern ones, otherwise they would contribute to an increase in the "p" value, which would lead to a dramatic reduction of SN lesions, which would probably lead to the clearance of Mtb. Another interesting point is that the percentage of SP infectious cases is not influenced by the Mtb lineage, it depends entirely on the historical period studied, meaning that the reduction of health status in the Neolithic was responsible for the marked increase the severity of TB. The better health status was important in the Paleolithic when we look at the percentage of Recovered and Infectious SN, as it shows a wider gap in the Paleolithic than in the Neolithic. This means that even when ancient lineages

were more virulent, because they had originated in the Paleolithic, they were well tolerated. On the other hand, modern lineages increased the percentage of people exposed regardless the historical period studied, confirming its higher capacity for dissemination.

2.3.- The SN Recovered cases were crucial for maintaining Mtb infection in the Paleolithic while the Neolithic era is marked by the entrance of SP lesions.

The evolution of the people in the different compartments over a thousand years using the continuous TBSpectr model to find the stationary distribution (Figure 4) shows that the SN Recovered compartment was the most important one for ensuring the persistence of Mtb infection. This led to the induction of a reduced percentage of infectious people with SN lesions. The impact of SP infectious cases was minimal in this period. The irruption of modern lineages led to a slight increase on these values, making the SP infectious values even more negligible, but noticeably increasing the number of people exposed, which increased to reach a similar percentage as the group of susceptible people.

This scenario changes radically in the Neolithic period when SP infectious cases irrupt dramatically, as shown in Figure 3. This is remarkable in the case of infections caused by ancient lineages. In the case of the modern ones this irruption is delayed by a parallel increase in SN lesions, although once established, the increase is faster in both cases. In this case the number of SN and SP infectious cases are similar in the stationary equilibrium, which allows a reduction of non-infected people (susceptible compartment). However, in the end it allows a faster growth of the global population, which can be seen by looking at the higher number of people in all compartments after the 1,000-year period and explains the predominance of modern lineages (Supplementary Figure 1).

2.4.-Persistence of Mtb infection required interrelations among hunter-gatherer groups in the Paleolithic while the risk of human extinction was negligible.

When interrogating the discrete TBSpectr model to evaluate the probability of Mtb infection clearance (Figure 5) it is clear that regardless of the lineage, its survival would be impossible in reduced human groups. Data show how a minimum of a 1,000-person community was necessary to maintain it during the Palaeolithic, and slightly less under the infection with modern lineages. This means that the groups of 50 hunter-gatherers had to interrelate, otherwise the infection would have disappeared. This factor was less important in the Neolithic due to the higher growth population rate. On the other hand, data on the capacity of Mtb infection to cause the extinction of humankind (Figure 6) shows that this was very low, roughly around 0.2% after 500 years of coevolution in a limited group of 50 people.

2.5.- The number of people infected per case and the fast progression to disease are the most important factors in maintaining TB in existence.

Sensitivity analysis (Figure 7) using a range of values per parameter shown in Table 2 analyse the influence of the different factors used to define the TBSpectr model. The most important ones are precisely the ones that we have discussed as differentiating ancient and modern Mtb lineages, i.e. the people infected per case/year (e) and rapid progression towards active TB (f), as these are the determinants of induction for all compartments of infected people. In this regard, the immunity factor (i) seems to have the same influence, but in this case has to be read inversely, as the lower the value the higher protection. It was interesting to confirm that the increase in the protective factor (p) increased the number of SN cases and reduced the SP ones, as expected. The reduction of infected cases by the higher mortality caused by TB (μTBsp) was also expected, as it reduces the chances of infection, thus causing an increase in the susceptible compartment. The increase of natality linked to the increase of natural mortality

(μ) is also expected as it is precisely what happens in the Neolithic. What is interesting to note is the positive correlation between the curation of SP infectious people (c_{sp}) and the number of SN infectious people, showing an obvious interrelation between both compartments. Finally, it is also interesting to see the corroboration of how the charge value (k), which decreases the bacillary load by a factor of 10, increases the chance of SN infectious cases developing from recovered cases. This links the importance of the bacillary load to the induction of SN or SP forms. The higher load should induce SP forms and a lower load SN forms.

3.-DISCUSSION.

Our model demonstrates how coevolution between Mtb and humanity has been possible. Even when molecular measurements point to the origin of the most recent common ancestor (MRCA) of Mtb emerging around 73,000 years BCE, it has been previously hypothesized that its origin is linked with the control of fire, around 300,000 to 400,000 BCE[36]. Furthermore, there is one report that claims the presence of *Leptomeningitis tuberculosa* in the endocranial surface of a hominid fossil with an estimated age of around 500,000 BCE in Kocabas (Turkey)[37]. Although the interpretation of this finding has been controversial[38], it could be hypothesized that before a complete settlement as a human parasite, *Mycobacterium* species have attempted several times to become the MRCA of the Mtb complex that we identify nowadays. In this sense, Gutierrez *et al* identified a very ancient ancestor (3,000,000 BCE) linked to the smooth tubercle bacilli (*M. canettii* strains), which are still isolated from human TB today[39]. This position is supported by looking at the evolution of the lipid composition of the mycobacterial cell wall. In this regard Jankute *et al* have theorized the origin of Mtb as a progressive increase in the hydrophobicity of the cell wall. Thus, the origin of Mtb complex would be *M. kansasii*, with a smooth morphology; a hydrophilic, environmental mycobacteria which acts as an opportunistic pathogen of several mammals, including humans. With the progressive loss of the polar sugars together with the acquisition of apolar ones, there was an evolution towards *M. canettii* and *canetti/tuberculosis* species to finally become the Mtb complex MRCA, and a human obligate pathogen[40].

Overall this means that Mtb is the result of thousands of years of evolution of environmental mycobacteria, living in cell free media (water and dust) or colonizing free living amoebas[41,42], moving to colonize the "pulmonary amoebas", as we can consider the alveolar macrophages, to finally becoming an obligate parasite thanks to its capacity to disseminate through aerosols[40]. But originally this parasitization had to be sustainable in the context of a low-density human population; based in small tribal groups with a necessary interrelation between them, as has been demonstrated by others[43], to avoid the clearance of the infection. Our data indicates that even by developing mild SN TB forms with low dissemination capacity, the obligate parasitization was possible. In fact, recent data on molecular epidemiology supports a higher impact of subclinical TB cases than expected[44], challenging the status of current diagnosis methodology, if we are to finally eradicate this infection. In fact, looking at the countries with the lowest TB incidence it appears that there is a long-lasting persistent low incidence of the infection[45], which is usually attributed to imported cases, but that we should also attribute to the original nature of Mtb infection. The persistence of Mtb in our tissues would also provide some evolutive advantage to humans, for instance by increasing trained immunity and allowing them to better control acute respiratory viral infections[46]. A sort of mutualism, the "old-friends" relationship that has been also linked to several colonizing microorganisms, through the balance of our inflammatory responses, which has led to the evolution of the human immune system[47,48]. Our data also indicates that it was after the change in the living conditions of humans and reduction of standard of living, which came with the Neolithic revolution, that there was an increase in TB severity and mortality. This took place despite the lower virulence

of the newly evolved modern lineages, which had a lower inflammatory capacity, but also had higher dissemination abilities[23].

How could the new Neolithic culture influence the development of more severe SP TB forms? The answer could lie in the neuroendocrine stress response. Evolutionarily speaking this is a very ancient response that can be detected in the first complex multicellular animals (i.e. fish). This reaction, known as the "fight or flight" reaction, increases secretion of glucocorticoids (GCs)[49]. Several studies have demonstrated that lower socioeconomical status is related to stress, and to increased levels of cortisol[50]. It is worth highlighting that with the onset of the agricultural revolution, social imbalance appeared and the transition to an unequal society far from the collaborative one of the Paleolithic [25,26]. Thus, the development of more severe SP TB forms can be attributed to a chronic increase on the levels of cortisol, instead to an increase in Mtb virulence as, on the contrary, modern lineages are less proinflammatory[51] and less prone to induce severe lesions. In a way this coincides with the concept of TB as a disease of the lower classes and a sign of unequal society [52]. There are several observations that supports this hypothesis; from the increased basal cortisol levels recorded in farmers in Kenya, who depend solely on agriculture for their income[53], or in non-politically influential men of the Bolivian Tsimane forager-horticulturalists[54]. Equally, studies in seven primate species showed that subordinate baboons had higher resting cortisol levels than did their dominant companions[55].

Glucocorticoids (GC) mobilize neutrophils and generate neutrophilia, increasing their life span by reducing their apoptosis, and increasing IL-1 levels[56]. Equally, oral administration of GC increases neutrophils in airway mucosa due to the increased expression of IL-8 and IFN-gamma inducible protein (IP-10) in the epithelia in asthmatic patients[57–59]. Furthermore, cortisol increase has a direct impact on the proinflammatory activation of neutrophils, as it also causes hyperglycaemia, which promotes NETosis in lesions[60]. This is in line with the "fight-or-flight" paradigm. The acute stress response serves as an endogenous psychophysiological adjuvant that enhances immune responses and has evolved by virtue of the fact that many stressful situations (aggression, accident) result in immune activation (against wounding or infection)[61]. Interestingly, this mechanism would also be the explanation of the sexual dimorphism detected in the TB incidence[62]. Even when there are no differences in basal levels, there are several studies concluding that men produce more circulating levels of cortisol than women in psychological stress tests [63–65]. This is the explanation for why major depression increases the risk of TB, but only in men, as observed in a nationwide population study in Korea[66].

How can we link the increase of GC and severe forms of TB? Recently, a new mechanism has been proposed, which links TB to a sudden inflammatory response led by neutrophils, thanks to the capacity of Neutrophilic Extracellular Traps (NETs) or NETosis for promoting extracellular bacillary growth within themselves[67–69]. This leads to the formation of new surrounding granulomas and overall coalescence, in a way resembling soap bubbles, this increases the size of the lesion, generating of a liquefacted necrosis and cavitation[70].

Our work sustains the hypothesis/idea that Mtb did not only evolve to become a competent aerosol disseminating pathogen among humans, but also the ability to remain sustainable among low density populations. This was possible thanks to its ability to generate minimal lesions (SN forms), and probably because there was some sort of evolutionary advantage to humans in becoming a mutualist microorganism, such as the stimulation of the innate immune response to respond to respiratory viral infections through the trained immune mechanism[71]. It was the cultural human changes in lifestyle, with the Neolithic Revolution, that broke this

balance and generated TB the major killer of humankind.

Overall, our data supports the concept that Mtb infection is highly adapted to persist and coevolve with humans. From a practical point of view, this means that its eradication would be very difficult because of its capacity to remain among us discretely, thus challenging the current diagnostic tools. It also emphasizes the poverty-related nature of the disease and the need to provide better global health status and greater equality to avoid severe forms of the disease in order to be able to reduce its terrible morbidity and mortality.

4.-METHODOLOGY.

4.1.- TBSpectr model.

We have designed a compartmental mathematical model based on a set of differential equations to describe the dynamics of the evolution of MtbC infection in the population, based on our previous study in several models[23].

The population is divided into several compartments according to their status with regards to the infection cycle: S, susceptible; E, non-infectious exposed; I_{SP}, smear-positive infectious; I_{SN}, smear-negative infectious; R_{SP}, recovered from a smear-positive TB course; R_{SN}, recovered from a smear-negative TB course. Newborn individuals appear at a rate π in the susceptible compartment. Mortality is given by μ when it is not caused by a TB, $\mu_{TB,SP}$ when it is caused by a SP tuberculosis, and $\mu_{TB,SN}$ when it is caused by a SN tuberculosis. Flows between compartments are shown in Figure 1 and given by this set of equations:

$$\frac{dS}{dt} = \pi + \delta E - \mu S - \beta IS \tag{1}$$

$$\frac{dE}{dt} = (1-f)\,\beta SI\ - \big(\mu + \delta + i(a+rI)\big)E \tag{2}$$

$$\frac{dI_{SP}}{dt} = f(1-p)\beta SI + i(1-p)(a+rI)E + (1-p)wi(a+rI)R - \big(\mu + \mu_{TB,SP} + c_{SP}\big)I_{SP} \tag{3}$$

$$\frac{dI_{SN}}{dt} = fp\beta SI + ip(a+rI)E + pwi(a+rI)R - \big(\mu + \mu_{TB,SN} + c_{SN}\big)I_{SN} \tag{4}$$

$$\frac{dR_{SP}}{dt} = c_{SP}I_{SP} - \big(\mu + wi(a+rI)\big)R_{SP} \tag{5}$$

$$\frac{dR_{SN}}{dt} = c_{SN}I_{SN} - \big(\mu + wi(a+rI)\big)R_{SN} \tag{6}$$

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} \tag{7}$$

Where $I = I_{nc} + I_c$ and $R = R_{nc} + R_c$.

The transmission rate β depends on the number of new infections caused by a particular SP or SN case (e_{SP} and e_{SN}), as well as on the proportion of each infectious compartment: $\beta =$

$\frac{1}{N}\frac{e_{SP}I_{SP}+e_{SN}I_{SN}}{I_{SP}+I_{SN}}$ [31]. The probability of showing rapid progression of the disease during the first-year post-infection or reinfection is given by f [72,73]. The parameter r provides the risk of disease caused by reinfection as $r = f\beta + a(1-f)\beta$. We consider a protective ratio i of 0.1 (i.e., those infected people that do not develop the disease have a protection against the onset of disease of at least 90%) [74]. The drainage of the infection on exposed individuals is given by δ [75,76], which is assumed to be reduced by the possibility of endogenous or exogenous reactivation of the infection, defined as a and r, respectively. Thus, bacillary drainage is defined as: $\delta = 0.1 - a - r$. Uys et al.[77]determined that recovered subjects have a sevenfold higher chance of developing disease, which is given by w in our model. The birth rate (π) is determined from the mean number of births per fertile woman/year (λ).

The assumptions behind each of the equations and values have been discussed at length previously[23]. The main novelty of this update of the model is the distinction between smear positive and smear negative infections. In this regard, we have introduced the protection factor p, which determines the percentage of active cases that show a smear negative course. The annual spontaneous cure (c_{SP} and c_{SN}) and dying ($\mu_{TB,SP}$ and $\mu_{TB,SN}$) rates depend on the SP or SN nature of the disease and is given by Ragonnet et al[33].

4.2.- Assessment of uncertainty and sensitivity in the system.

The uncertainty and sensitivity analysis was of the TBSpectr model was performed as described in [78]. We used a Latin Hipercube Sampling (LHS) technique to generate 1,000 different parameter sets that are representative of the parameter space (sampling-based method). Parameters were explored between the values shown in Table 2. The Partial Rank Correlation Coefficient (PRCC) was computed at each time step for each of the parameters and susceptible, exposed, infected, recovered and total populations, as well as the annual incidence and death rates. We also computed the final PRCC between input parameters and TB clearance and community extinction, using the discrete resolution (see below). This analysis allows for the assessment of the individual effect of each parameter on each outcome, with a linear discount of the effects of the uncertainty on the rest of the parameters.

4.3.- Continuous and discrete resolution of the models.

The continuous TBSpectr model was numerically integrated with Matlab using the Euler method, with an integration step of 1/10 years. As a result of the integration, we obtain the dynamics of each of the model's variable.

As we discussed in our previous paper[23], the limited size of some of the communities studied suggests the suitability of exploring a discrete resolution of the model, using natural numbers to describe the variables' dynamics. In such discrete resolution, which is also based on the Euler's integration method, we convert each of the flows at each integration step into a natural number using Poisson random distribution. This use of randomness on the flows' rounding makes it possible that two communities with the same initial conditions and model's parameters diverge on their evolution. In particular, there is a chance that a certain community achieves the clearance of the infection, while other communities remain affected by TB or can even be extinct because of the pathogen.

5.-FIGURES.

Figure 1. TBSpectr model. Each compartment refers to the set of individuals by disease status: Susceptible, Exposed, Infected, Recovered. New-born individuals are assumed susceptible. A TB infection can remain latent (**E**), or can directly develop into infectious active TB (**I**). The latent TB infection can become active through endogenous reactivation or exogenous reinfection. Patients with active TB can naturally recover (**R**) becoming non-infectious. We identify two categories in I and R, according to the spectrum of the disease. Sputum negative (**SN**) and positive (**SP**), to distinguish between a weaker and greater extension of the disease. The driver for the evolution towards both forms of the disease depends on the value of a protecting factor (p) that depends on the health status of the host. Equally, we have included a factor depending on the bacillary load (k) linked to sputum negative cases. Latent infected persons (**I**) can drain the bacilli, lose the immunity and become susceptible (**S**). Recovered persons can relapse to active TB through endogenous reactivation or exogenous reinfection.

Figure 2. Relation between the protective factor and natality. Adjustment of natality (**A**) and effective natality understood as the number of 15 year-old surviving children per women (**B**) using the parameters of the TBSpectr model and the accepted growth population rate for the Paleolithic (0.0003%/year) and the Neolithic (0.1%/year). Colored lines represent the values for the Paleolithic period and the infection with ancient (orange) and modern (violet) variants of Mtb; and the Neolithic period and the infection with ancient (blue) and Modern (yellow) variants of Mtb. Dots of each corresponding color show the value of the protective factor (p) chosen in each case.

Figure 3. Evolution of the percentage of individuals in each SEIR compartment in relation with the protective value (p) according to the continuous TBSPectr model. Pictures show the evolution obtained in Susceptible (A), Exposed (B), Infected SN (C), Infected SP (D), Recovered SN (E) and Recovered SP (F). Fractions are independent from initial conditions. Colored lines represent the values for the Paleolithic period and the infection with a (orange) and modern (violet) variants of Mtb; and the Neolithic period and the infection with ancient (blue) and modern (yellow) variants of Mtb. Dots of each corresponding color show the value of the protective factor (p) chosen in each case.

Figure 4. Evolution of the population in the continuous TBSpectr model towards the stationary state. Pictures show the projections of 1,000 simulations in a group of 100 people with a random initial distribution among compartments ($S_0 \in [0, 100]$, $E_0 \in [0,40]$, I_{c0}, I_{n0}, R_{c0}, $R_{n0} \in [0,100-S_0-E_0]$, the sum of all compartments is equal to 100) during 1,000 years of evolution. The thick lines correspond to the central scenario with $S_0=80$, $E_0=20$ and other compartments starting at zero. Evolution is drawn for the Paleolithic period and the infection with ancient (A) and modern (B) variants of Mtb; and the Neolithic period and the infection with ancient (C) and modern (D) variants of Mtb. Colour lines represent the different compartments, Susceptible (blue), Exposed (orange), Infected SN (yellow), Infected SP (violet), Recovered SN (green) and Recovered SP (cerulean blue). Bold lines represent the average of all lines per compartment, and values after 1000 years show the equilibrium fraction. For reference there is a grey doted horizontal line marking the presence of 1 people (10^0 $\log_{10}$).

Figure 5. Relation between the size of the human group and the clearance of the Mtb infection. Heatmap of the end values for 1,000 year's evolution on the TBSpectr discrete model using the initial conditions in each compartment found in the equilibrium phase shown

previously (Figure 4). For reference we have included a vertical dotted red line at the time where there is a 100% clearance, a horizontal dotted red line to reference the evolution in a population size of 100 people and a white line at the population size where there is a 0% clearance in the Paleolithic period under the infection of Mtb ancient lineages. Clearance means the lack of population in the Exposed, Infectious and Recovered compartments.

Figure 6. Relation between the size of the human group and the extinction of humankind. Heatmap of the end values during 1,000 year's evolution on the TBSpectr discrete model using the initial conditions in each compartment found in the equilibrium phase shown previously (Figure 4). Extinction means the disappearance of humankind in the group explored.

Figure 7: Sensitivity analysis
Heatmap showing Partial Rank Correlation Coefficient on the TBSpectr discrete model analyzing 1,000 simulations. Influence of the evolution in Infected people per case/year (e), fast progression (*f*), immunity (i), bacillary charge (k), natural mortality (μ), reactivation factor in recovered (w), annual population growth rate (gr), curation in Sputum Positive (c_{SP}), mortality caused by TB (μ_{TB}), and protective factor (p), in the evolution of Clearance in groups of 100 (CL100) and 1,000 (CL10000) people, Extinction in groups of 100 (E100) and 1,000 (EX1000) people, and the equilibrium fraction of Susceptible (S), Exposed (E), Infectious Sputum Negative (ISN), Infectious Sputum Positive (ISP), Recovered Sputum Negative (RSN) and Recovered Sputum Positive (RSP) compartments.

6.-COMPETING INTERESTS.

The authors declare no potential conflict of interest.

7.-AKNOWLEDGEMENTS.

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8.- AUTOR CONTRIBUTIONS.

PJC has conceived the work, written and structured the paper and designed the TBSpectr model; **CP** has refined the TBSpectr model; **MC** has implemented the model in Matlab and run the sensitivity analysis and the simulations; All authors have worked in the analysis and interpretation of the data.

9.-TABLES.

Table 1. Parameters and references.

Parameter	Values		Sources
	Paleolithic	Neolithic	
Annual population growth rate (gr)	0.003%	0.1%	18,79,80
Natality (λ)	0.032	0.044	
15 years old surviving children / women	2.11	2.33	
Natural mortality/year (μ)	1/33	1/26.5	81,82
Protection factor severity progression (p)	0.488 (A) 0.677 (M)	0.096 (A) 0.268 (M)	assayed
Mortality/year caused by TB (μ_{TB})	0.389(SP) / 0.025 (SN)		33
Infected people per case/year (e)	A= 10(SP)/1(SN); M= 20(SP)/2(SN)		34,83
Bacillary charge (k)	0.1		34
Fast progression (f)	0.099(A)/0.0825(M)	0.1238(A)/0.1031(M)	72
Reactivation from infection (a)	f · 0.3		
Bacillary drainage and immunity reduction (δ)	0.1-a-r		75,76
Reduced progression due to immunity (i)	0.1		84
TB natural cure (c)	0.231 (SP) / 0.130 (SN)		33
Increased progression in Recovered (w)	7		77

Where SP: Sputum positive; SN: Sputum negative; A: Ancient Strain; M: Modern Strain

Table 2: Sensitivity analysis.

Parameter	Paleolithic value	Neolithic value	Sensitivity analysis range
λ	0.032	0.044	[0.03 0.05]
μ	0.03030	0.03846	[0.0286 0.04]
p	0.488 (A) 0.677 (M)	0.096 (A) 0.268 (M)	[0 1]
μ_{TB}	0.389(SP) / 0.025 (SN)		[0.02 0.4]
e	A= 10(SP)/1(SN); M= 20(SP)/2(SN)		[1 20]
f	0.099(A)/0.0825(M)	0.1238(A)/0.1031(M)	[0 0.13]
i	0.1		[0.05 0.5]
c	0.231 (SP) / 0.130 (SN)		[0.1 .3]
w	7		[1 7]
a	0.0297(A)/0.02475(M)	0.03714(A)/0.03093(M)	[0 0.038]

Where SP: Sputum positive; SN: Sputum negative; A: Ancient Strain; M: Modern Strain

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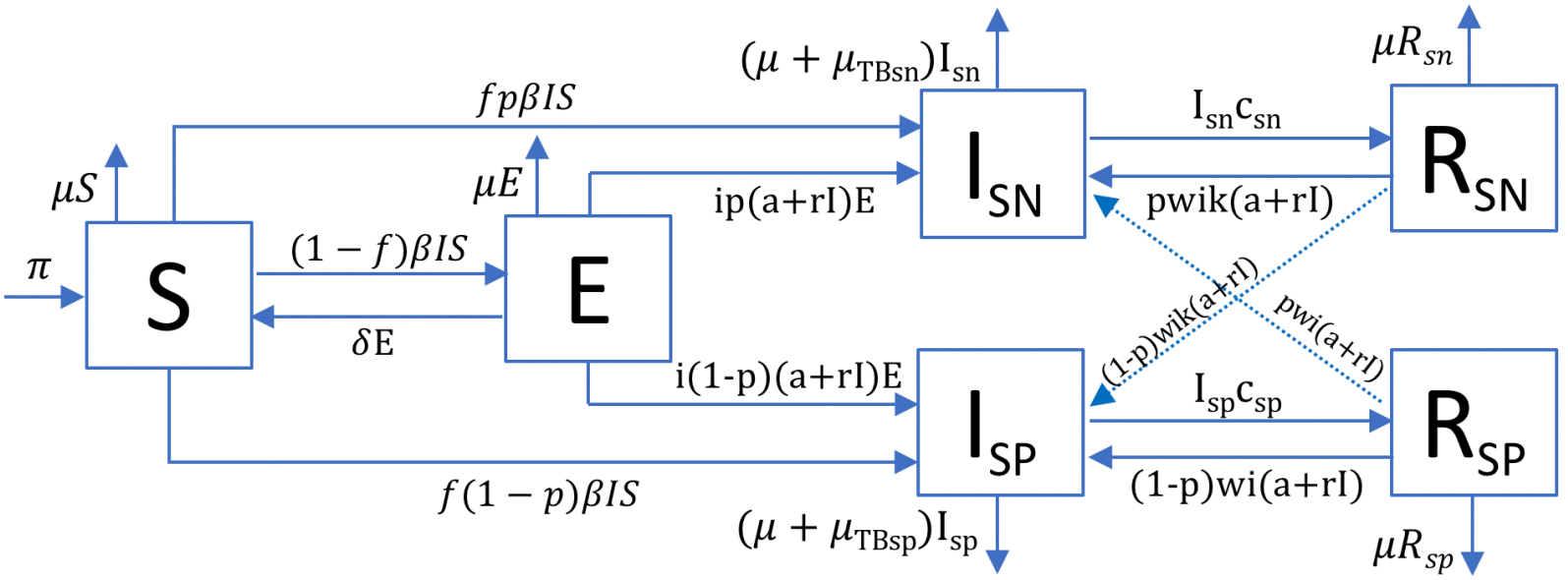

$\mu + \mu_{TBsn})I_{sn}$
μR_{sn}
$fp\beta IS$
μS
μE
$I_{sn}c_{sn}$
I_{SN}
R_{SN}
ip(a+rI)E
pwik(a+rI)
π
S
$(1-f)\beta IS$
E
δE
(1-p)wik(a+rI)
pwi(a+rI)
i(1-p)(a+rI)E
$I_{sp}c_{sp}$
I_{SP}
R_{SP}
(1-p)wi(a+rI)
$f(1-p)\beta IS$
$(\mu + \mu_{TBsp})I_{sp}$
μR_{sp}

Figure 1

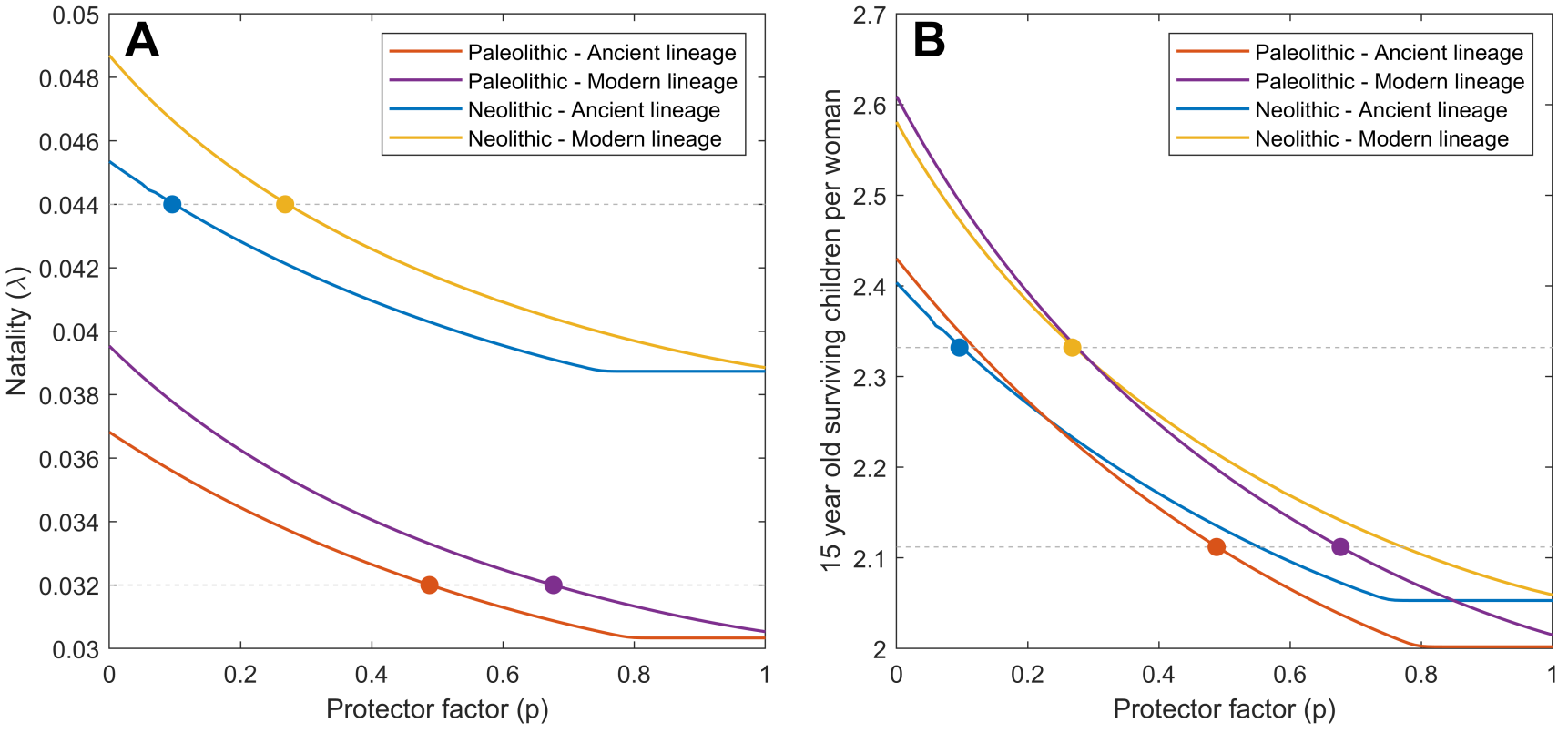

A
Paleolithic - Ancient lineage
Paleolithic - Modern lineage
Neolithic - Ancient lineage
Neolithic - Modern lineage
Natality (λ)
0.05
0.048
0.046
0.044
0.042
0.04
0.038
0.036
0.034
0.032
0.03
0
0.2
0.4
0.6
0.8
1
Protector factor (p)
B
Paleolithic - Ancient lineage
Paleolithic - Modern lineage
Neolithic - Ancient lineage
Neolithic - Modern lineage
15 year old surviving children per woman
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2
0
0.2
0.4
0.6
0.8
1
Protector factor (p)

Figure 2

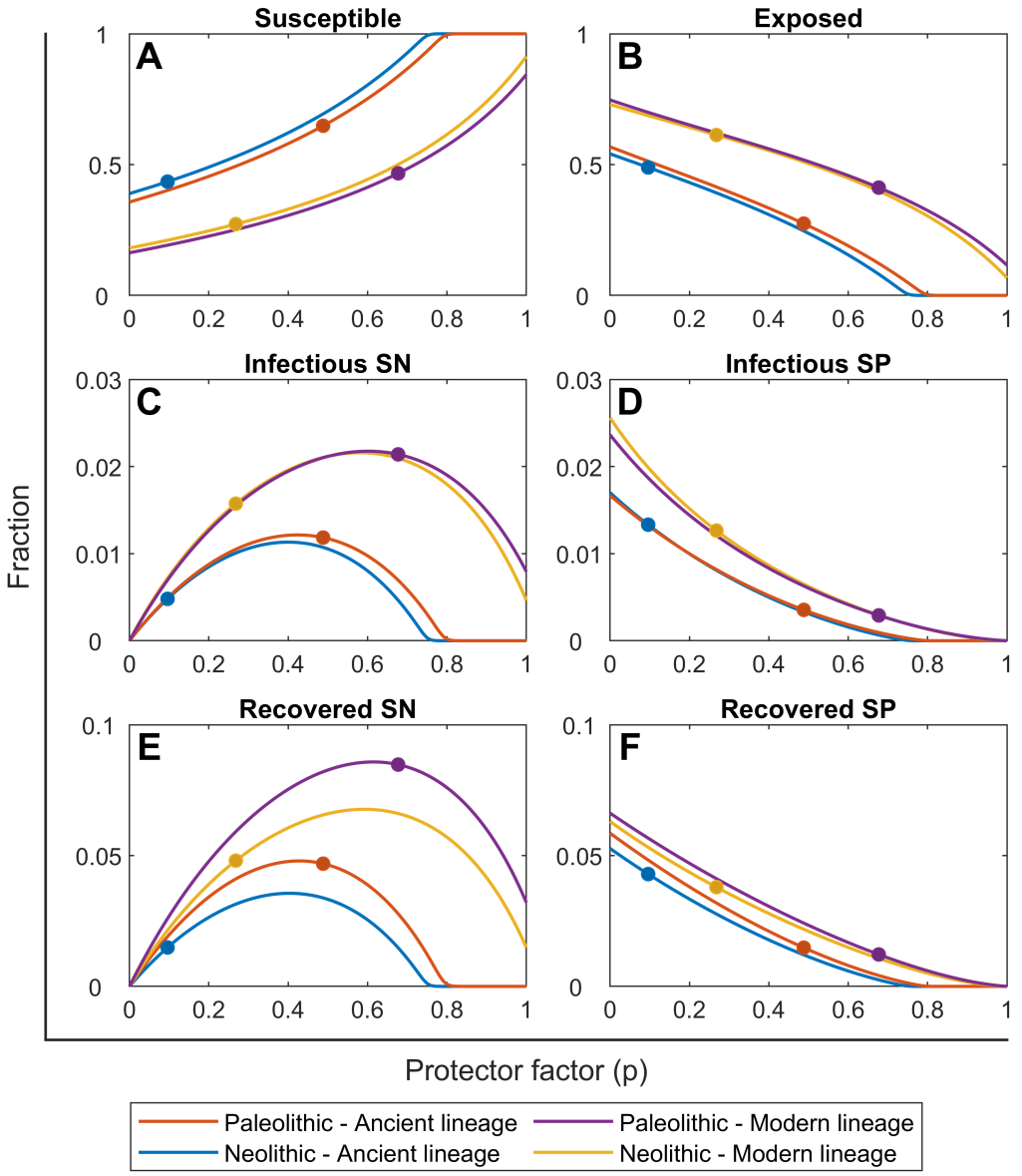

Susceptible
Exposed
Infectious SN
Infectious SP
Recovered SN
Recovered SP
A
B
C
D
E
F
Fraction
Protector factor (p)
Paleolithic - Ancient lineage
Paleolithic - Modern lineage
Neolithic - Ancient lineage
Neolithic - Modern lineage

Figure 3

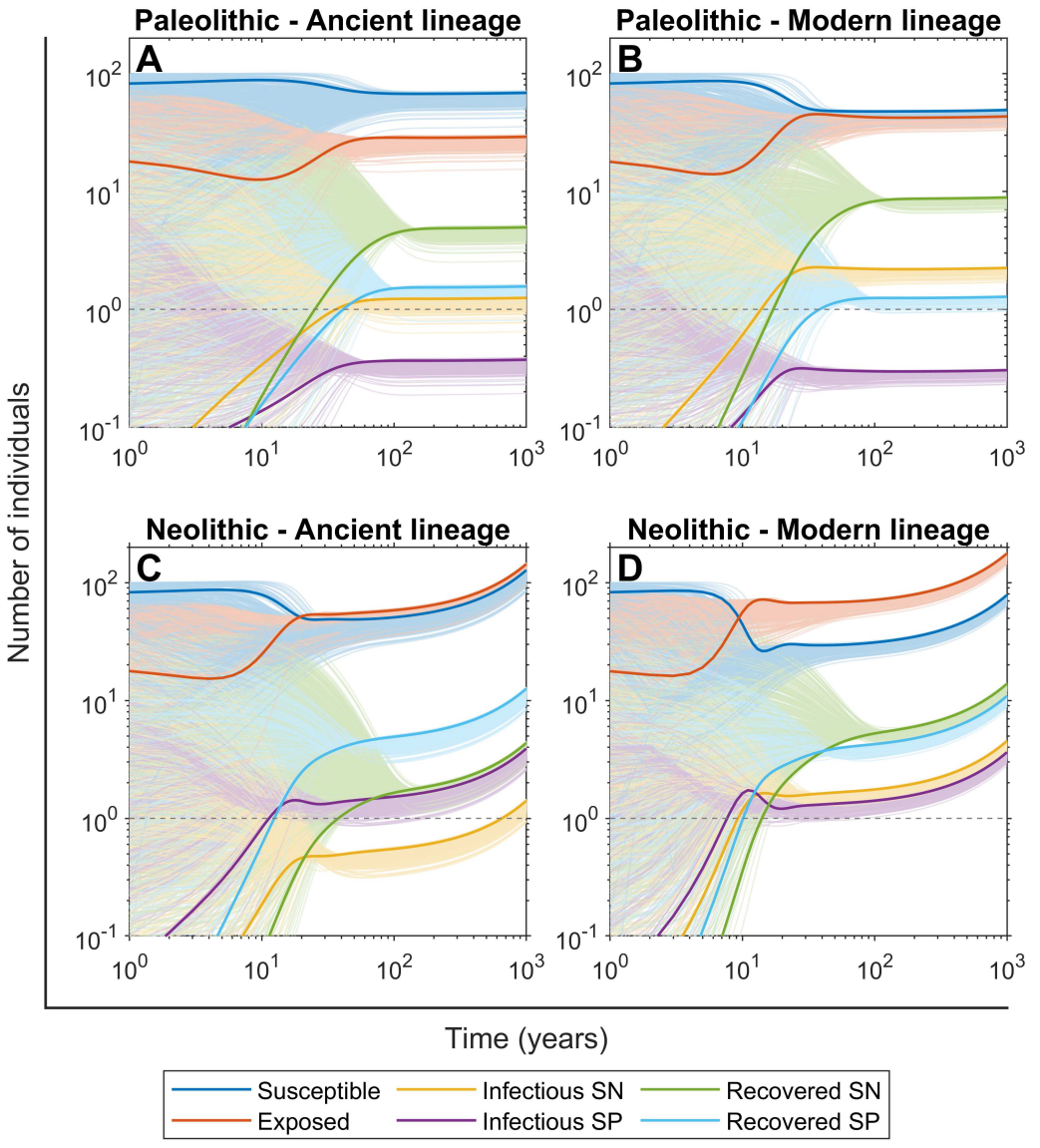

Paleolithic - Ancient lineage
Paleolithic - Modern lineage
Neolithic - Ancient lineage
Neolithic - Modern lineage
A
B
C
D
Number of individuals
Time (years)
Susceptible
Exposed
Infectious SN
Infectious SP
Recovered SN
Recovered SP

Figure 4

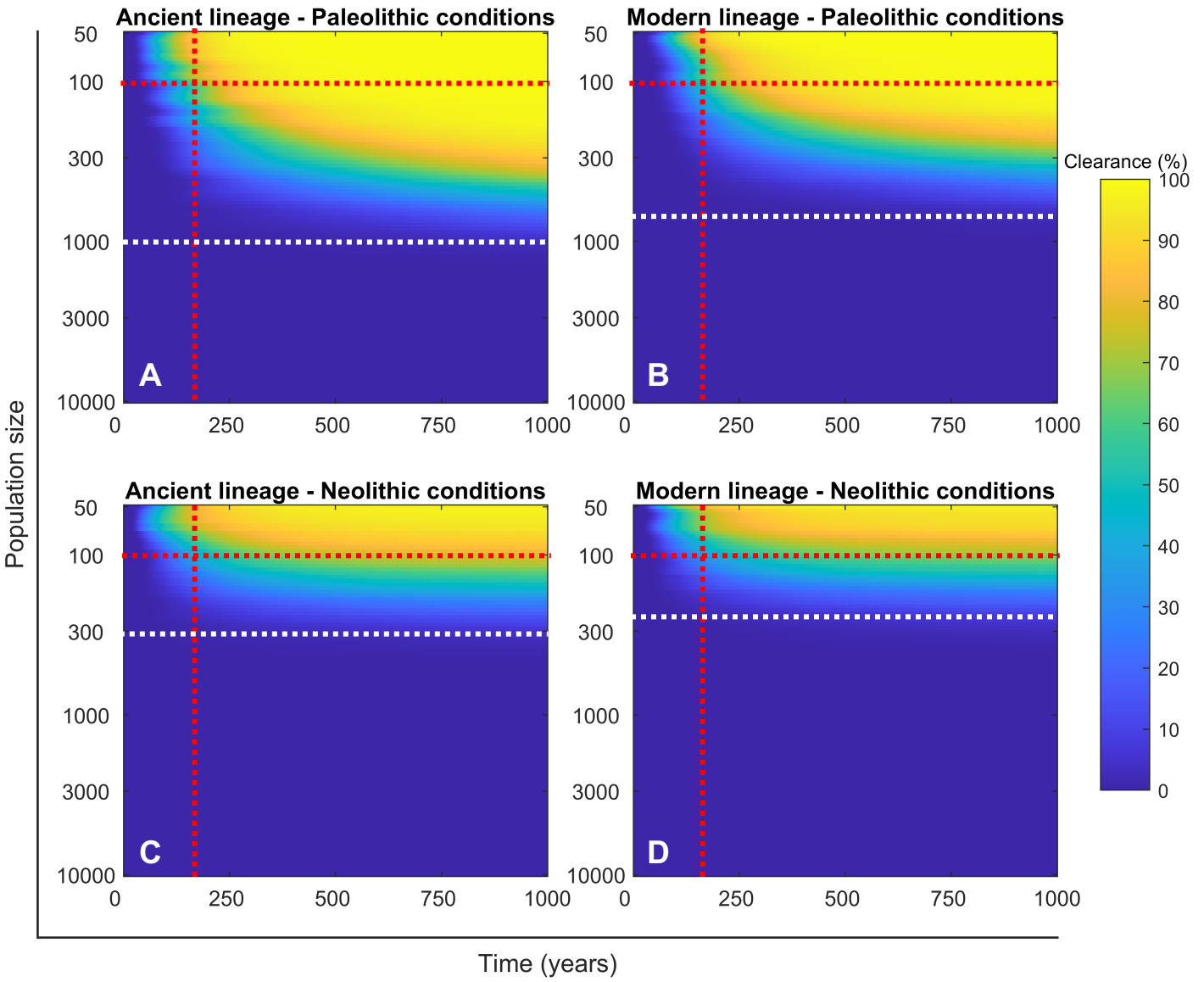

Ancient lineage - Paleolithic conditions
Modern lineage - Paleolithic conditions
Ancient lineage - Neolithic conditions
Modern lineage - Neolithic conditions
A
B
C
D
Population size
50
100
300
1000
3000
10000
0
250
500
750
1000
Time (years)
Clearance (%)
100
90
80
70
60
50
40
30
20
10
0

Figure 5

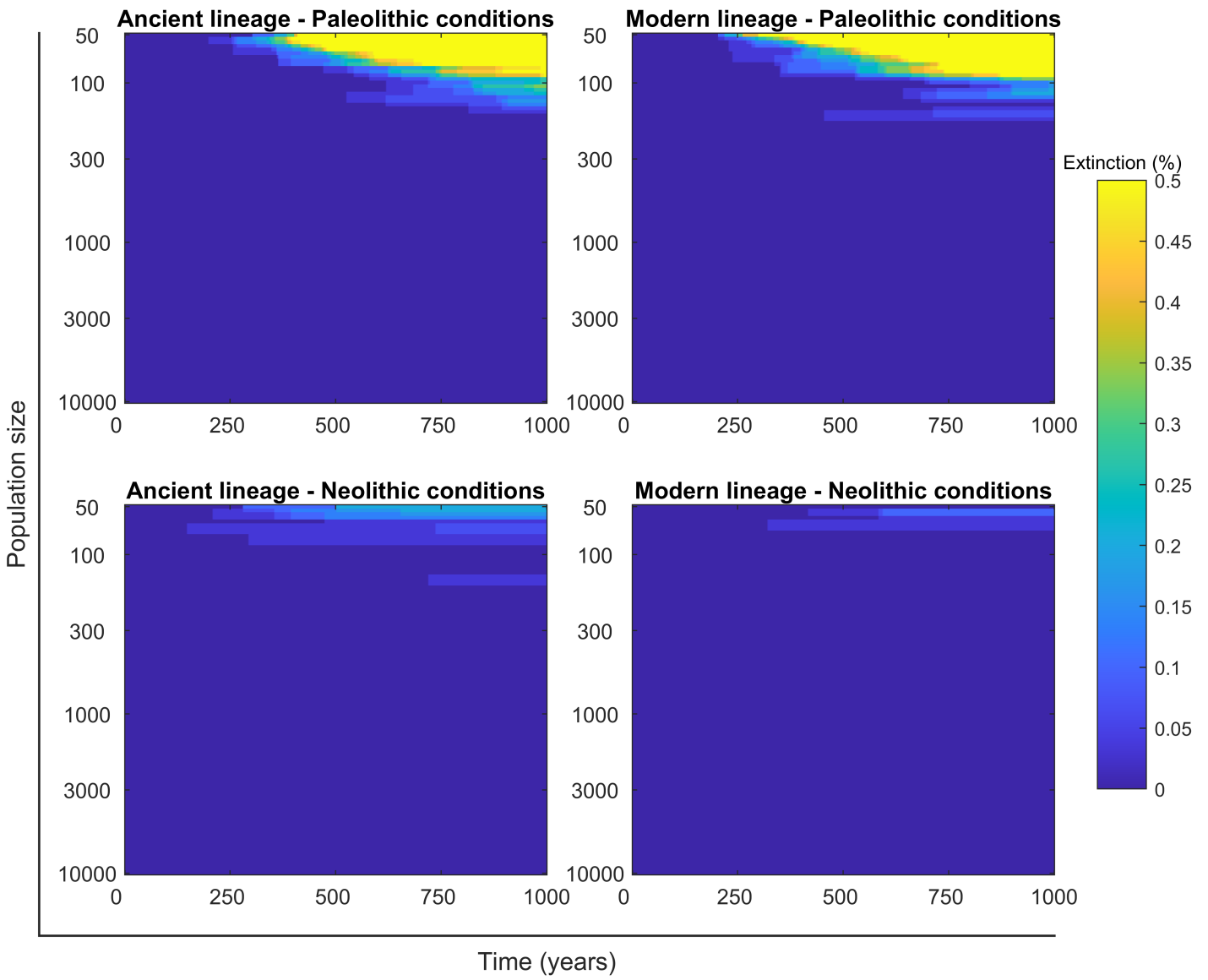

Ancient lineage - Paleolithic conditions
Modern lineage - Paleolithic conditions
Ancient lineage - Neolithic conditions
Modern lineage - Neolithic conditions
Population size
50
100
300
1000
3000
10000
0
250
500
750
1000
Time (years)
Extinction (%)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0

Figure 6

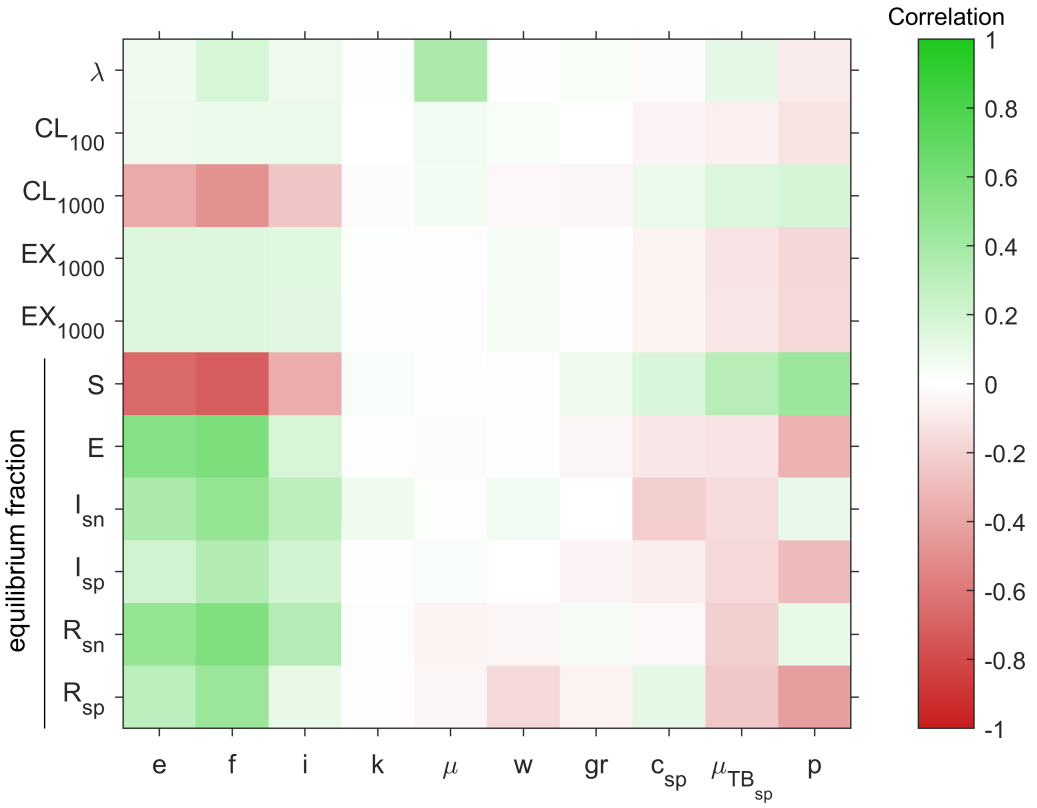
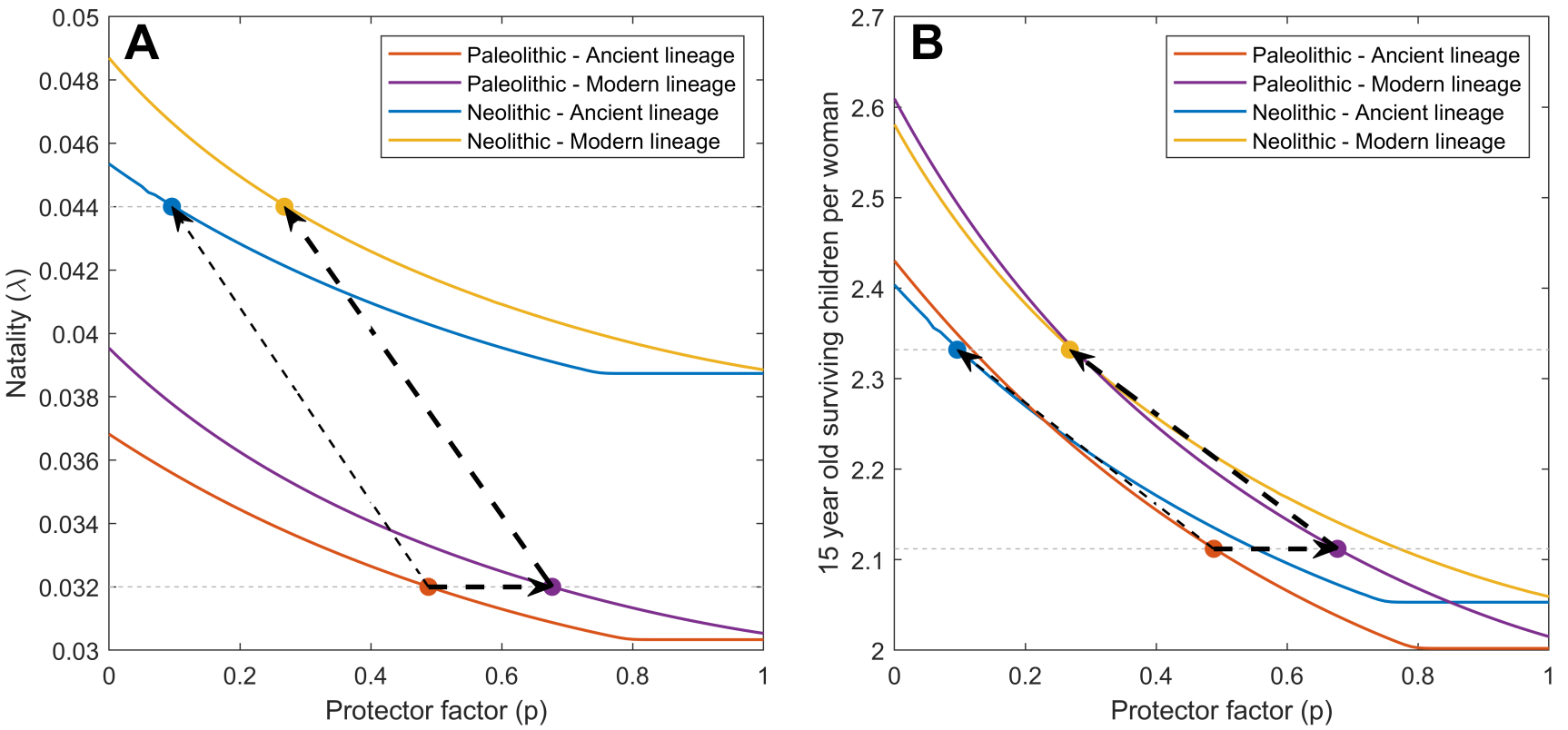

Correlation
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
λ
CL100
CL1000
EX1000
EX1000
S
E
Isn
Isp
Rsn
Rsp
equilibrium fraction
e
f
i
k
μ
w
gr
csp
μTBsp
p

Figure 7

The origin and maintenance of tuberculosis is explained by its subclinical course, the Neolithic revolution being the trigger for its devastating deadly drift.

Pere-Joan Cardona, Martí Català, Clara Prats.



Supplementary Figure 1. Hypothetical evolution of the Mtb lineages in relation between the protective factor and natality. Adjustment of natality (**A**) and effective natality understood as the number of births surviving more than 15 years old (**B**) using the parameters of the TBSpectr model and the recon growth population grow for the Paleolithic (0.0003%/year) and the Neolithic (0.1%/year). Colored lines represents the values for the Paleolithic period and the infection with Ancient (orange) and Modern (violet) lineages of Mtb; and the Neolithic period and the infection with Ancient (blue) and Modern (yellow) lineages of Mtb. Dots of each corresponding color show the value of the protection factor (p) chosen in each case.
Arrows show the evolution of Mtb lineages with the protector factor. The thicker ones show the mainstream evolution from the Ancient towards the Modern lineages favored by its decreased virulence, increasing the host protector factor which was maintained when the Neolithic revolution irrupted with poorer health conditions. The thinner arrow shows the pathway of ancient lineages, impacting only in those people with worse health conditions (lower p), thus being less competitive.

Figures

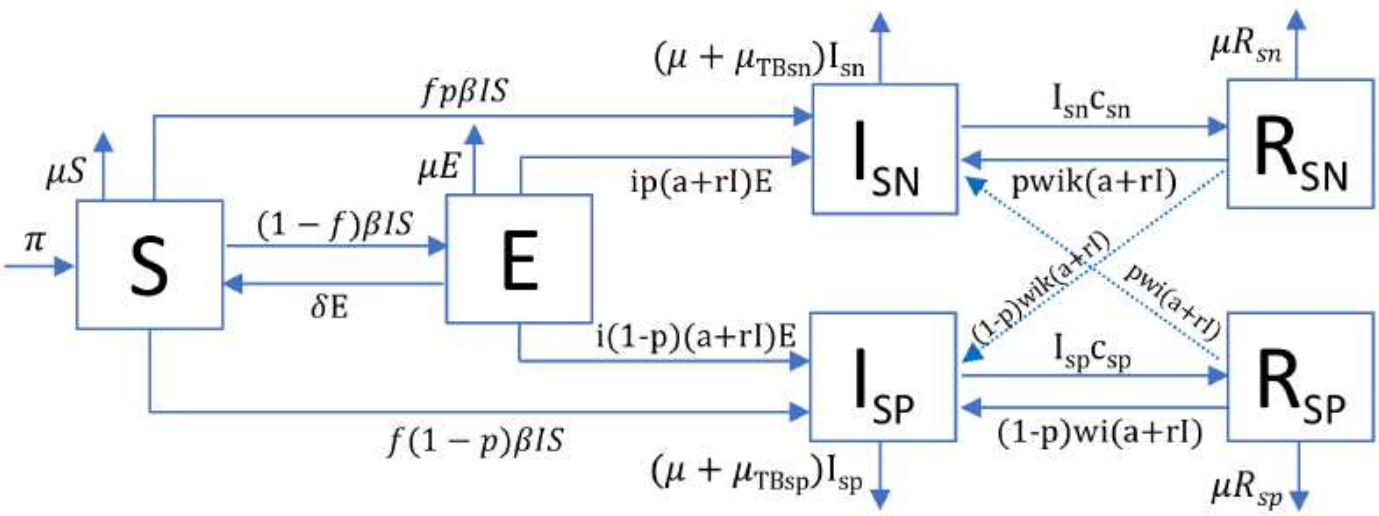


Figure 1

TBSpectr model. Each compartment refers to the set of individuals by disease status: Susceptible, Exposed, Infected, Recovered. New-born individuals are assumed susceptible. A TB infection can remain latent (E), or can directly develop into infectious active TB (I). The latent TB infection can become active through endogenous reactivation or exogenous reinfection. Patients with active TB can naturally recover (R) becoming non-infectious. We identify two categories in I and R, according to the spectrum of the disease. Sputum negative (SN) and positive (SP), to distinguish between a weaker and greater extension of the disease. The driver for the evolution towards both forms of the disease depends on the value of a protecting factor (p) that depends on the health status of the host. Equally, we have included a factor depending on the bacillary load (k) linked to sputum negative cases. Latent infected persons (I) can drain the bacilli, lose the immunity and become susceptible (S). Recovered persons can relapse to active TB through endogenous reactivation or exogenous reinfection.

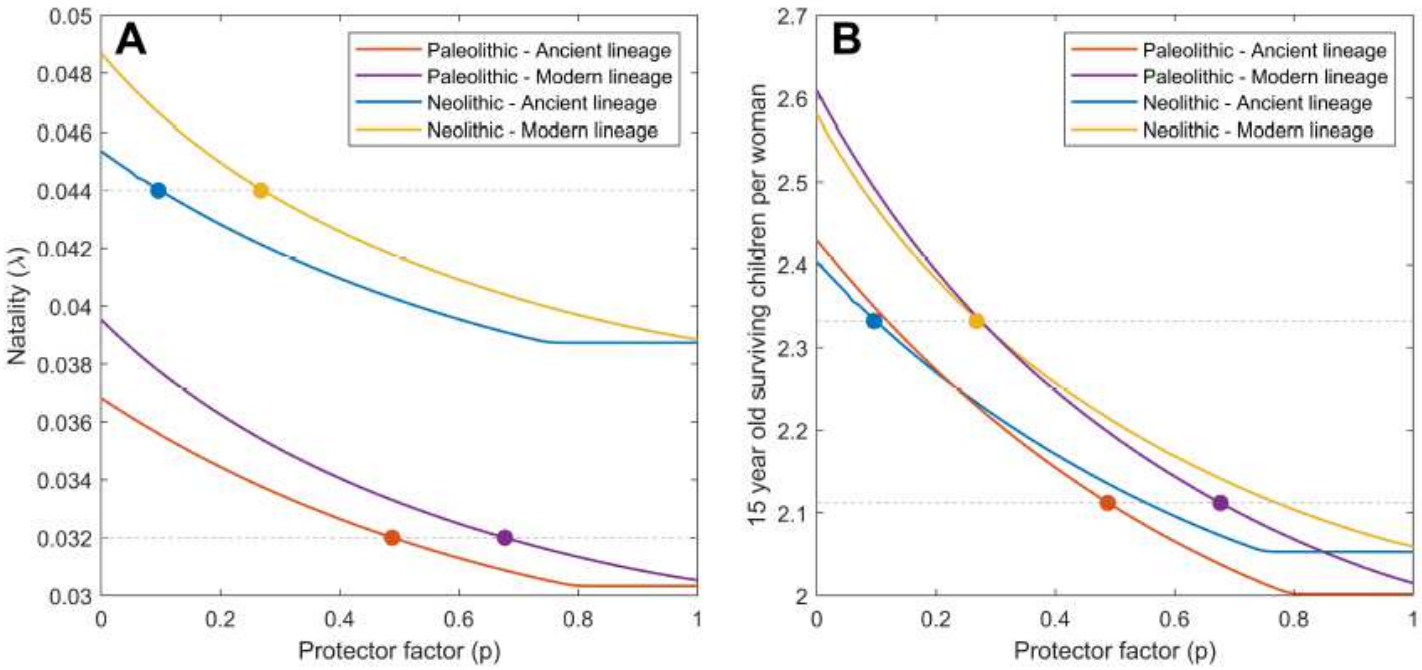


Figure 2

Relation between the protective factor and natality. Adjustment of natality (A) and effective natality understood as the number of 15 year-old surviving children per women (B) using the parameters of the TBSpectr model and the accepted growth population rate for the Paleolithic (0.0003%/year) and the Neolithic (0.1%/year). Colored lines represent the values for the Paleolithic period and the infection with ancient (orange) and modern (violet) variants of Mtb; and the Neolithic period and the infection with ancient (blue) and Modern (yellow) variants of Mtb. Dots of each corresponding color show the value of the protective factor (p) chosen in each case.

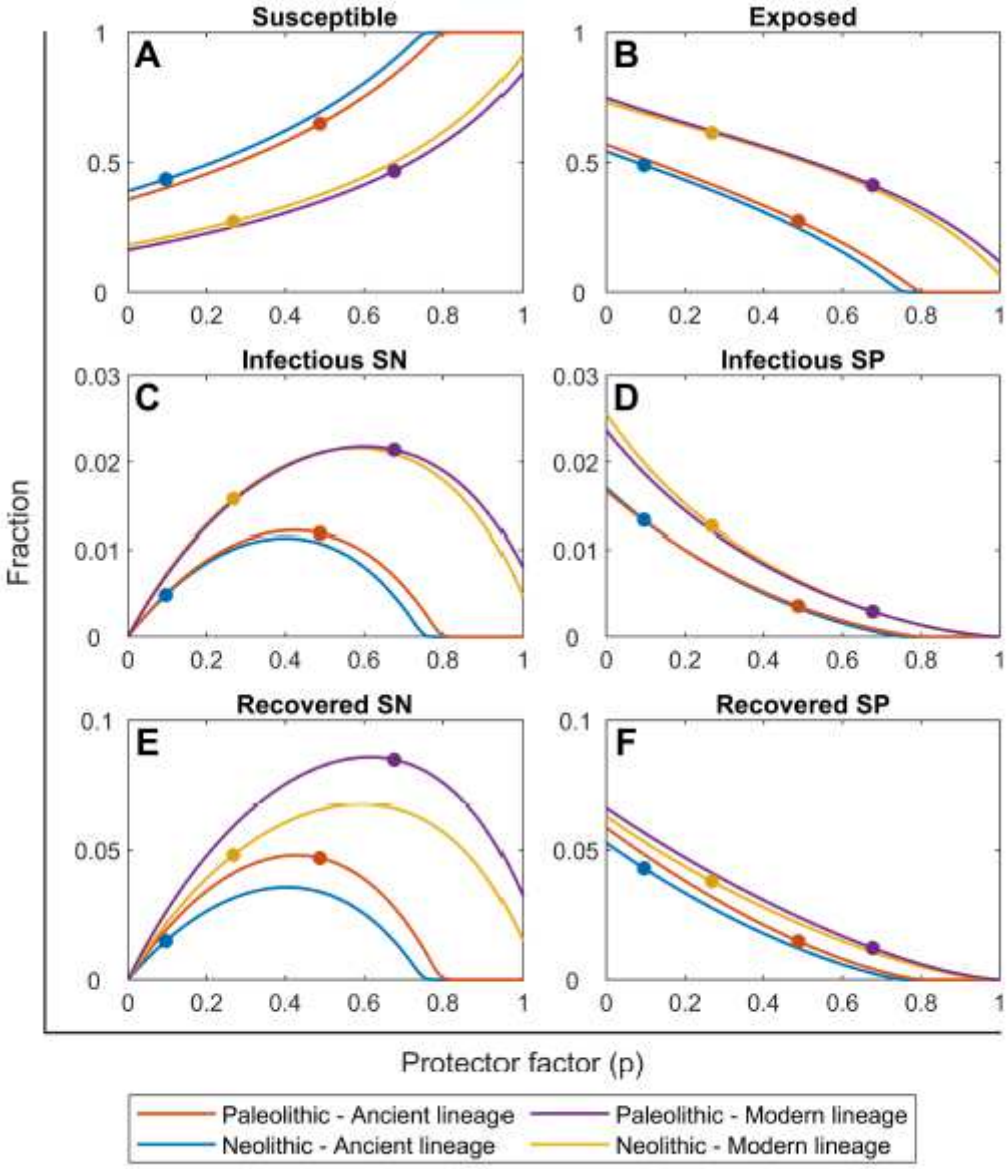


Figure 3

Evolution of the percentage of individuals in each SEIR compartment in relation with the protective value (p) according to the continuous TBSPectr model. Pictures show the evolution obtained in Susceptible (A), Exposed (B), Infected SN (C), Infected SP (D), Recovered SN (E) and Recovered SP (F). Fractions are independent from initial conditions. Colored lines represent the values for the Paleolithic period and the infection with a (orange) and modern (violet) variants of Mtb; and the Neolithic period and the infection with ancient (blue) and modern (yellow) variants of Mtb. Dots of each corresponding color show the value of the protective factor (p) chosen in each case.

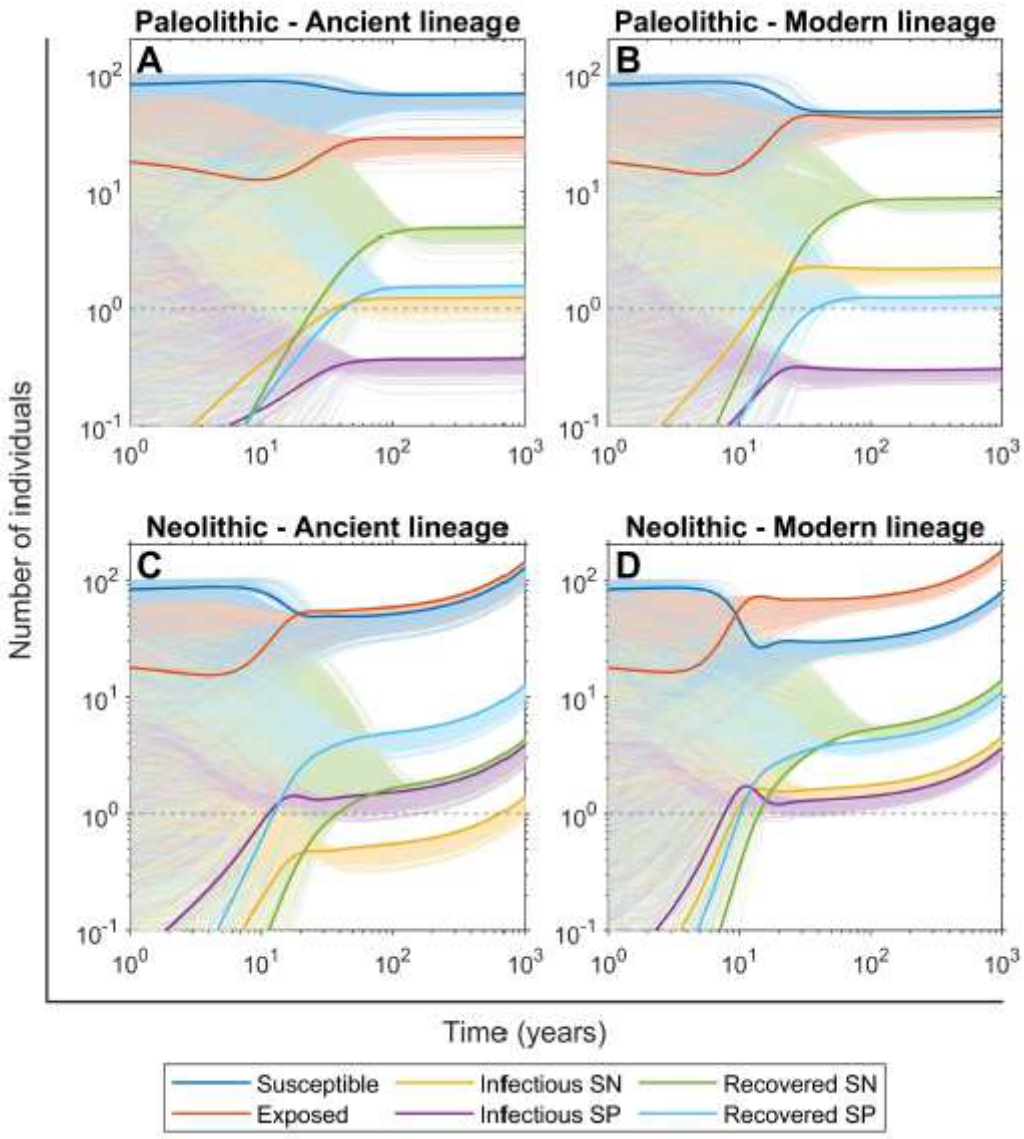


Figure 4

Evolution of the population in the continuous TBSpectr model towards the stationary state. Pictures show the projections of 1,000 simulations in a group of 100 people with a random initial distribution among compartments (S0∈[0, 100], E0∈[0,40], Ic0, In0, Rc0, Rn0∈[0,100-S0-E0], the sum of all compartments is equal to 100) during 1,000 years of evolution. The thick lines correspond to the central scenario with S0=80, E0=20 and other compartments starting at zero. Evolution is drawn for the Paleolithic period and the infection with ancient (A) and modern (B) variants of Mtb; and the Neolithic period and the infection with ancient (C) and modern (D) variants of Mtb. Colour lines represent the different compartments, Susceptible (blue), Exposed (orange), Infected SN (yellow), Infected SP (violet), Recovered SN (green) and Recovered SP (cerulean blue). Bold lines represent the average of all lines per compartment, and values after 1000 years show the equilibrium fraction. For reference there is a grey doted horizontal line marking the presence of 1 people (100 log10).

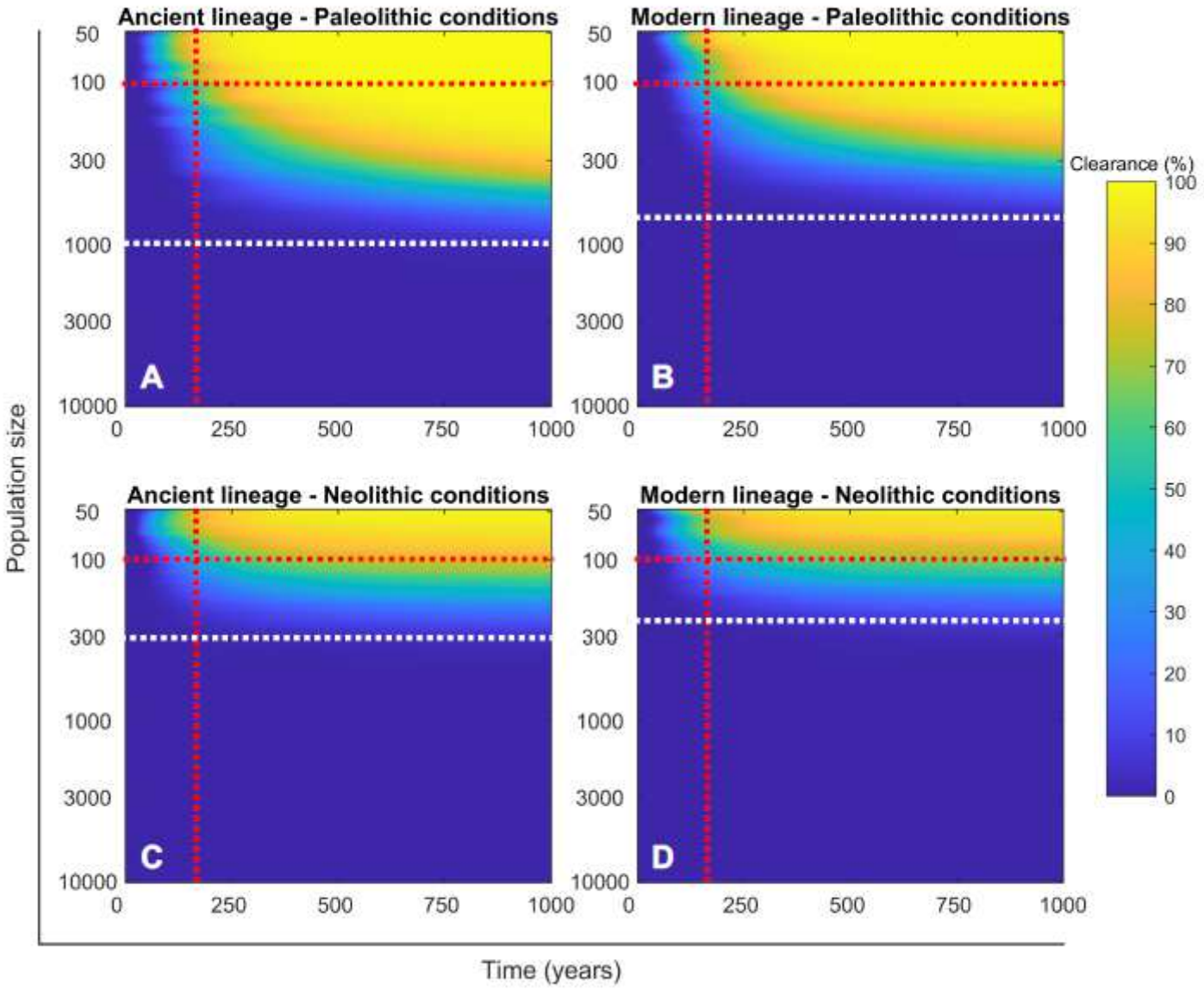


Figure 5

Relation between the size of the human group and the clearance of the Mtb infection. Heatmap of the end values for 1,000 year's evolution on the TBSpectr discrete model using the initial conditions in each compartment found in the equilibrium phase shown previously (Figure 4). For reference we have included a vertical dotted red line at the time where there is a 100% clearance, a horizontal dotted red line to reference the evolution in a population size of 100 people and a white line at the population size where there is a 0% clearance in the Paleolithic period under the infection of Mtb ancient lineages. Clearance means the lack of population in the Exposed, Infectious and Recovered compartments.

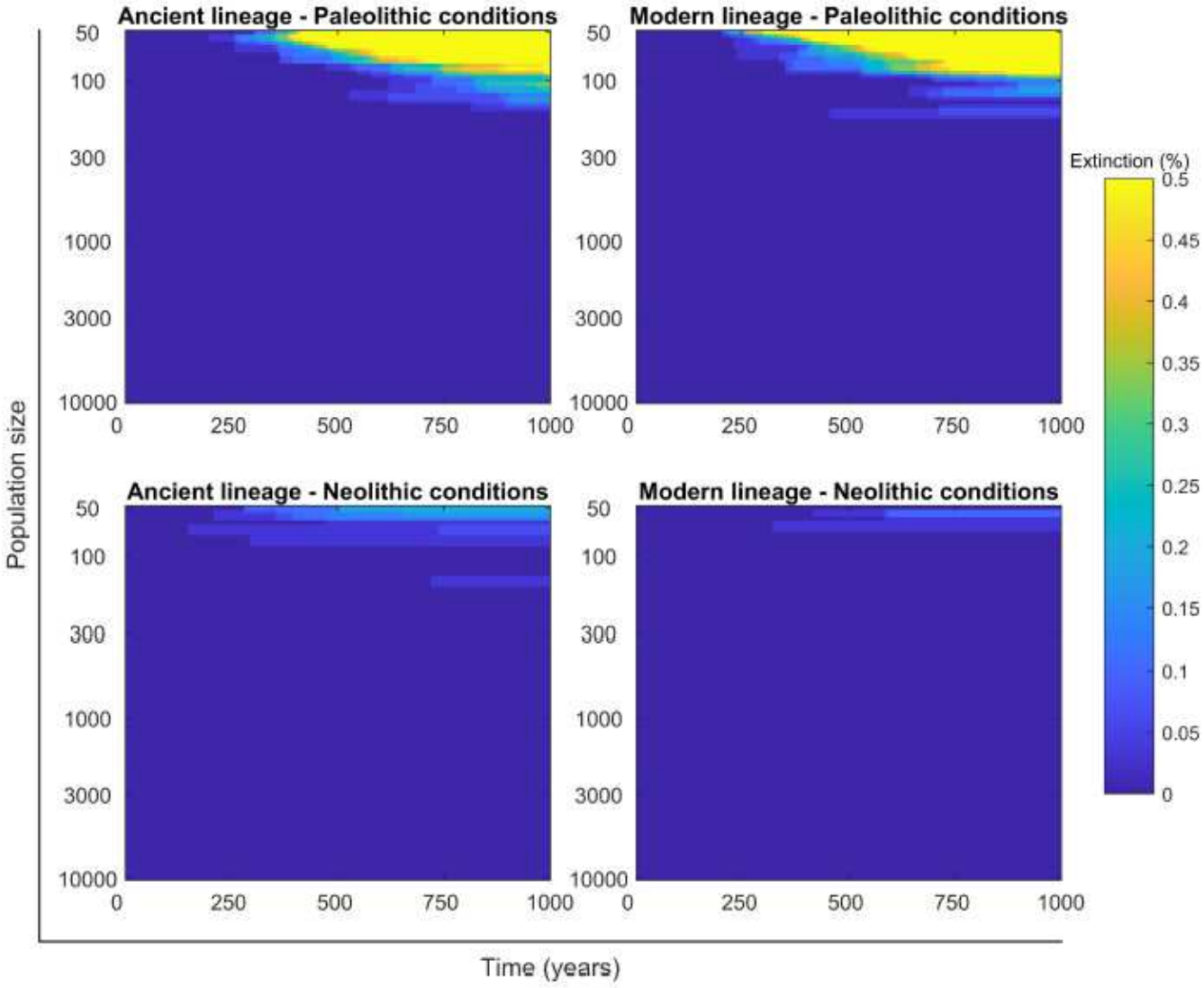


Figure 6

Relation between the size of the human group and the extinction of humankind. Heatmap of the end values during 1,000 year's evolution on the TBSpectr discrete model using the initial conditions in each compartment found in the equilibrium phase shown previously (Figure 4). Extinction means the disappearance of humankind in the group explored.

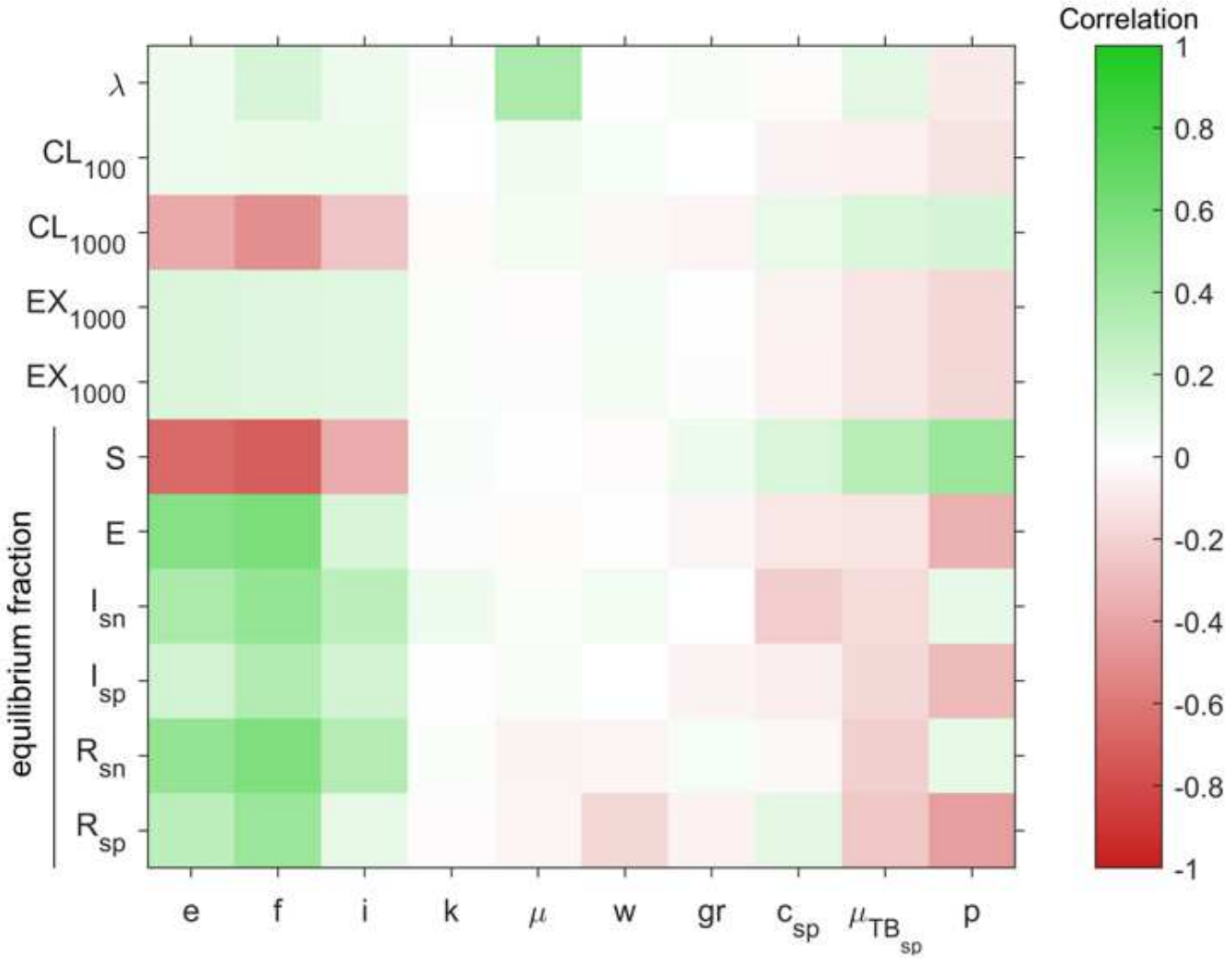


Figure 7

Sensitivity analysis Heatmap showing Partial Rank Correlation Coefficient on the TBSpectr discrete model analyzing 1,000 simulations. Influence of the evolution in Infected people per case/year (e), fast progression (f), immunity (i), bacillary charge (k), natural mortality (□), reactivation factor in recovered (w), annual population growth rate (gr), curation in Sputum Positive (cSP), mortality caused by TB (□TB), and protective factor (p), in the evolution of Clearance in groups of 100 (CL100) and 1,000 (CL10000) people, Extinction in groups of 100 (E100) and 1,000 (EX1000) people, and the equilibrium fraction of Susceptible (S), Exposed (E), Infectious Sputum Negative (ISN), Infectious Sputum Positive (ISP), Recovered Sputum Negative (RSN) and Recovered Sputum Positive (RSP) compartments.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FiguresTBSpectrSuppl1.pdf