Genetic analysis of longevity in specialized lines of rabbits

Análisis genético de la longevidad en líneas especializadas de conejos

Ph.D. Thesis

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“Fear Allah wherever you are, follow a bad deed with a good deed and it will erase it, and behave with good character toward the people”

The Prophet Muhammad (ﷺ)

DEDICATION

This dissertation is dedicated to my late father, Prof. Gamal Fawzy, and to my late mother, Laila Mohamed, who always had confidence in me and offered me encouragement and support in all my endeavours; may Allah bless their souls, and I want to say

﴿ ***O my Lord! Have mercy upon them both, as they brought me up when I was young*** ﴾ *The Holy Qur'an, Chapter 17-Al-Isra': Verse 24.*

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ABSTRACT

The global objective of the present thesis was to study the functional longevity defined as length of productive life (LPL) in five Spanish specialized lines of rabbit. Four of them were maternal lines (A, V, H and LP) founded on different criteria and being selected for litter size at weaning. The other was the paternal line R, founded and selected for postweaning daily gain from 28 to 63 d. These lines are reared in a closed nucleus of selection located in the farm of the Department of Animal Science, Polytechnic University of Valencia. The data used were collected during the programmes of selection from their foundation till the 44th, 39th, 10th, 8th and 32nd generations of selection for lines A, V, H, LP and R, respectively. For a suitable genetic evaluation of animals in the nucleus, some common culling criteria in commercial farms are not considered; i.e. does with low levels of production or no strong reproductive delay are not culled. So, the doe's LPL reflects directly its functional longevity.

Chapter 3, aimed to check the genetic heterogeneity for longevity between the five lines estimating the additive variance and the corresponding effective heritabilities. As well as to test the genetic importance of time-dependent factors such as positive palpation order (OPP), physiological status (PS) and number of kits born alive (NBA) on the genetics of longevity. This point has been assessed using four different Cox proportional hazard models; the first one (Model 1) included all the previous factors in addition to the year-season effect, the inbreeding coefficient effect and finally the animal effect as random factor. The remaining three models were the same as Model 1 but excluding OPP (Model 2), or PS (Model 3), or NBA (Model 4). Estimates of the additive variance for longevity were compared across models. Moreover, the effects of the different levels of each time-dependent factor were studied. The complete data set comprised 15,670 does with records 35.6 % having censoring data, and the full pedigree file involved 19,405 animals. Using the four models, data of each line was analysed separately and a joint analysis of all lines was conducted as well, replacing the year-season by line-year-season combination. The heritability estimates for longevity in the five lines were low and ranged from 0.02±0.01 to 0.14±0.09, and consequently, it is not

recommended to include this trait as selection criteria in rabbit breeding programs. Despite of the large variation of the heritability estimates, the corresponding $HPD_{95\%}$ always overlapped and consequently the hypothesis of all lines having the same heritability cannot be discarded. Comparing the additive variance estimates of the four models, it was observed that by correcting for PS 51, 39, 38, 83 and 75% of the additive variance in lines A, V, H, LP and R, respectively, was removed. In the contrary, correcting for OPP or NBA led to negligible changes in the additive variance. So, part of the genetic differences for longevity could be related to the way in which the females cumulate risk associated to the life term pass through the different physiological statuses. The highest genetic trends of the hazard were observed for lines A and H, showing the important role of the natural selection especially in the lines with low longevity. The risk of death or culling decreases as OPP advanced, with the highest risk during the first two parities, this could be explained as in the first two parities the does are still growing and the kindling would be an important risk factor. Non-pregnant-non-lactating females are those under the highest risk compared to the other levels of PS, this could be an indication of low fertility and/or health problems of the doe. Also, from the results of PS, it seems that the lactation status of the doe had relatively higher importance than their reproductive status. The does which had zero NBA had the highest risk, apart for this special figure (zero NBA) the risk decreased as NBA increased. As in these populations culling based on production traits is not carried out, so, the greater risk of culling related to low litter sizes could be associated with underlying pathological disorders. It should be noted that in line LP the magnitude of contrasts between the different levels of OPP, PS and NBA was higher than those in the other lines, this may be considered as a range effect due to the foundation criteria used in this line that increased its longevity and the range of the factors affecting the trait.

Chapter 4 intended to estimate the genetic and environmental correlations between longevity and two prolificacy traits (number of kits born alive (NBA) and number of kits alive at weaning (NW)). Furthermore, to estimate the genetic and environmental correlations between longevity and the percentage of days that the doe spent in the

different physiological statuses with respect to its entire productive life. This was done to try to explain the changes in the additive variance when removing PS from the model of analysis of longevity (Model 3 in Chapter 3). The complete pedigree file comprised 19,405 animals. The datasets included records on 15,670 does which had 58,329 kindlings and 57,927 weanings. The heritability estimates ranged from 0.05±0.02 to 0.11±0.01 for NBA and from 0.04±0.02 to 0.12±0.01 for NW. These estimates were in general low values and tended to decrease from birth to weaning. The lowest estimates were observed in line H (0.05±0.02 for NBA and 0.04±0.02 for NW) which may be in part due to the foundation criteria followed to create this line - hyperprolificacy. In general the genetic correlations between each of NBA and NW, and the hazard were ranged from low to very low, and the only line for which it can be said these genetic correlation to be different from zero was the LP line. However, taking into account that the reported errors of correlations underestimated the standard errors, these correlation estimates can be considered not significantly different from zero. Consequently, longevity and prolificacy cannot be considered as antagonistic objectives of selection in the rabbit breeding programs. The heritability estimates for the percentage of days in each physiological status were low values and ranged from 0.02±0.02 to 0.11±0.05, 0.01±0.03 to 0.06±0.03, 0.01±0.01 to 0.10±0.03, 0.03±0.02 to 0.10±0.09, 0.06±0.03 to 0.19±0.06 and 0.01±0.03 to 0.11±0.03 for the percentage of days that the female spent in the status: before palpation test/non lactating, pregnant/non lactating, non-pregnant/lactating, before palpation test/lactating, pregnant/lactating, and non-pregnant/non lactating, respectively. Regarding the correlations between longevity and the percentage of days the doe spent in each physiological status, there were evidences of non-negligible genetic correlations between the two traits. Although, the standard errors of the estimates did not allow proving that these correlations were significantly different from zero.

Chapter 5 purposed to compare the five lines at their foundation and at fixed time periods during their selection programs. The first comparison was done at the origin of the lines, involving the complete data set, and using a genetic model (CM) including the

additive values of the animals, so the effect of selection was considered. The second comparison was done at fixed times through the selection process, comprising the last 18 months when at least four lines shared the same environmental and management conditions (from March 1997 to September 1998 for lines A, V, H and R; and from March 2011 to September 2012 for lines A, V, LP and R). For the second comparison the same model as the first comparison was used, but excluding the additive effects from the model of analysis (IM), and involving only the data corresponding to each period, so the differences between the lines included the additive values of the animals. The lines V, H and LP showed at foundation a substantial superiority over line A. The line R had higher risk of death or culling with relevant differences when compared to V, H and LP lines. The maximum relative risks were observed between the lines LP and R (0.239), and between LP and A (0.317). This means that at foundation it was 0.239 and 0.317 times more likely for a LP doe to be culled/died than for a R and A female, respectively. For the comparisons at fixed times, the pattern of the differences between the A line and the others was similar to those observed at foundation. But, in general, as the selection process evolves, the differences between the lines were changed and mostly reduced, this demonstrate the importance of natural selection in the lines of low longevity at their foundation, which improves their average longevity. For the four maternal lines, the predicted differences estimated using the CM model match pretty well the differences estimated using the IM model which is an indication that the complete genetic model was suitable to analyse the data set of these rabbit populations. This was not the case for the paternal line R, line with the lowest censoring rate, and reproductive performances very different to the maternal lines. From this study, it can be concluded that using as criteria for founding new lines the fulfilment of the morphological characteristics of a given breed, in the case of the A line New Zealand White, does not seem appropriate to guarantee good longevity performances. In the contrary criteria directly related to production or longevity performances, as in the case of the LP line, are more appropriate to grant good longevity of the newly founded population.

RESUMEN

El objetivo global de la presente tesis fue estudiar la longevidad funcional en cinco líneas españolas de conejos, el carácter se definió como la longitud de la vida productiva (LPL). Cuatro de las líneas estudiadas fueron maternales (A, V, H y LP) fundadas por diferentes criterios, pero todas ellas seleccionadas por tamaño de camada al destete. La quinta fue la línea paternal R, fundada y seleccionada por ganancia diaria post-destete entre 28-63 d. Estas líneas se han desarrollado en un núcleo de selección situado en las instalaciones del Departamento de Ciencia Animal de la Universidad Politécnica de Valencia. Los datos utilizados fueron recogidos durante los programas de selección desde la fundación hasta la 44ª, 39ª, 10ª, 8ª y 32ª generación de selección para las líneas A, V, H, LP y R, respectivamente. Para una adecuada evaluación genética de los animales en el núcleo, algunos criterios de eliminación que se utilizan habitualmente en las granjas comerciales no se consideraron; es decir, las conejas con niveles bajos de producción, baja prolificidad o con cierto retraso reproductivo no se eliminaban. De esta manera, la LPL de la coneja reflejó directamente su longevidad funcional.

En el Capítulo 3, dirigido a comprobar la heterogeneidad genética de la longevidad entre las 5 líneas, se estimaron las varianzas aditivas y sus correspondientes heredabilidades efectivas. Y además se evaluó la importancia de factores dependientes del tiempo, como el orden de la palpación positiva (OPP), el estado fisiológico (PS) y el número de gazapos nacidos vivos (NBA) sobre el determinismo genético de la longevidad. Para ello se utilizaron 4 modelos de Cox de riesgos proporcionales; el primer modelo (Modelo 1) incluyó todos los factores anteriormente señalados, además del efecto del año-estación, el efecto de la consanguinidad y, finalmente, el valor aditivo de los animales como efecto aleatorio. Los otros tres modelos fueron igual que el Modelo 1 pero excluyendo OPP (Modelo 2), o PS (Modelo 3), o NBA (Modelo 4). Los datos de longevidad estaban referidos a 15,670 conejas y tuvieron una tasa de censura de 35.6%. La genealogía completa involucró a 19,405 animales. Se realizaron análisis tanto de cada línea por separado como del conjunto de todas las líneas utilizando los 4 modelos. En el

análisis conjunto se sustituyó el año-estación por la combinación línea-año-estación. Las estimas de heredabilidad efectiva (Modelo 1) para la longevidad en las 5 líneas fueron bajas y variaron de 0.02±0.01 a 0.14±0.09, y, en consecuencia, no se recomienda incluir este carácter como criterio de selección en los programas de mejora del conejo. A pesar de la gran variación de las estimas puntuales de heredabilidad, los correspondientes intervalos $HPD_{95\%}$ siempre se solaparon y por lo tanto la hipótesis de que todas las líneas tengan la misma heredabilidad no pudo descartase. Comparando las estimas de varianza aditiva de los 4 modelos, se observó que la exclusión de PS incrementó la varianza aditiva, aproximadamente, en un 51, 39, 38, 83 y 75% en las líneas A, V, H, LP y R, respectivamente. Sin embargo, la exclusión de OPP o NBA no condujo a cambios relevantes en las estimas de la varianza aditiva. Así, se pude concluir que parte de las diferencias genéticas de la longevidad podrían estar relacionadas con la forma en que la hembra acumula riesgo debido a que va pasando de un estado fisiológico a otro y en el tiempo que pasa en cada uno de estos estados. Es decir que el patrón de PS por el que pasa cada hembra a lo largo de su vida tendría un cierto determinismo genético y que éste estaría correlacionado con el de la longevidad. Las tendencias genéticas más pronunciadas se observaron para las líneas A y H, en concordancia con el mayor papel que la selección natural debe tener sobre las líneas de más baja longevidad media (línea A) y también en concordancia con las mayores estimas de heredabilidad observadas (línea H). El riesgo de muerte o eliminación disminuía a medida que avanzaba el OPP, observándose el riesgo más alto durante los primeros dos partos, partos en los que las conejas todavía están creciendo lo que sería un factor de riesgo importante. El nivel No-Gestante-No-Lactante de PS tuvo el mayor riesgo en comparación con los otros niveles. Este nivel se interpreta como indicador de baja fertilidad y/o problemas de salud de la coneja. En relación a los otros niveles de PS parece que en general el estado lactacional de las conejas (lactante o no lactante) tiene una mayor influencia en la definición del riesgo a que están sometidas las conejas que su estado reproductivo (gestante, no gestante, desconocido). Las conejas que tenían cero NBA tuvieron el mayor riesgo de muerte o eliminación, aunque para el resto de niveles de NBA se apreció una disminución del riesgo a medida que aumenta la prolificidad. En estas poblaciones no se lleva a cabo eliminación por producción por lo tanto el mayor riesgo relacionado con tamaños de camada bajos podría estar asociado con trastornos patológicos subyacentes. Cabe señalar que, en la línea LP, la magnitud de los contrastes entre los diferentes niveles de OPP, PS y NBA fue mayor que en las otras líneas, lo que puede ser considerado como un efecto de rango debido al criterio de fundación utilizado en esta línea que aumentó su longevidad y por tanto también el rango de los factores que le afectan.

En el capítulo 4, se estimaron las correlaciones genéticas y ambientales entre la longevidad y dos caracteres de prolificidad [número de gazapos nacidos vivos (NBA) y el número de destetados (NW)]. El fichero de datos incluyó 58,329 partos y 57,927 destetes. También se estimaron las correlaciones entre longevidad y el porcentaje de días que la coneja pasó en los diferentes estados fisiológicos con respecto a la totalidad de su vida productiva. El objetivo de este segunda estimación de correlaciones era el de explicar los cambios observados en las estimas de la varianza aditiva de longevidad al eliminar del modelo el PS (Modelo 3 en Capítulo 3). Con respecto a las prolificidad las estimas de heredabilidad variaron de 0.05±0.02 a 0.11±0.01 para el NBA y de 0.04±0.02 a 0.12±0.01 para el NW. En general estas estimas fueron bajas y tendieron a disminuir desde el nacimiento hasta el destete. Las estimas más bajas fueron en la línea H y esto puede ser consecuencia del criterio de fundación seguido en esta línea. La única línea para la que se puede decir que la correlación genética entre NBA o NW y el riesgo fue significativamente diferente de cero fue la línea LP. Por lo tanto, la longevidad y la prolificidad no pueden considerarse como objetivos antagónicos de selección. Las estimas de heredabilidad del porcentaje de días en cada estado fisiológico fueron bajas y variaron de 0.02±0.02 a 0.11±0.05, 0.01±0.03 a 0.06±0.03, 0.01±0.01 a 0.10±0.03, 0.03±0.02 a 0.10±0.09, 0.06±0.03 a 0.19±0.06 y de 0.01±0.03 a 0.11±0.03 para el porcentaje de días que la coneja pasó en los estados antes de la palpación/no lactante, gestante/no lactante, no gestante/lactante, antes de la palpación/lactante, gestante/lactante y no gestante/no lactante, respectivamente. En cuanto a las correlaciones entre longevidad y los porcentaje de días que la hembra pasó en cada estado fisiológico, hubo evidencias de correlaciones genéticas no despreciables entre los dos caracteres, si bien los errores estándar de las estimas no permitieron demostrar que estas correlaciones fueran significativamente diferentes de cero. Por lo tanto, la hipótesis planteada en el capítulo 3 para explicar los cambios observados en las estimas de heredabilidad al no considerar el PS en el modelo no puede descartarse.

En el capítulo 5 se compararon las longevidades medias de las 5 líneas en su fundación y en períodos de tiempo determinados durante su proceso de selección. La comparación de las líneas en el origen, utilizó todos los datos y un modelo genético (CM) que incluía los valores aditivos de los animales, por lo que se consideró el efecto de la selección a partir de la fundación. La comparación en tiempos fijos se hizo en periodos correspondientes a los 18 últimos meses en que al menos cuatro líneas compartían las mismas condiciones ambientales y de manejo (desde marzo de 1997 hasta septiembre de 1998 (líneas A, V, H y R) y desde marzo 2011 hasta septiembre 2012 (líneas A, V, LP y R)). En esta comparación se utilizó el mismo modelo que en la anterior, pero excluyendo los efectos aditivos del modelo de análisis (IM), utilizando sólo los datos correspondientes a cada período, por lo que las diferencias entre las líneas incluían los cambios debidos a la selección. Las líneas V, H y LP mostraron una superioridad sustancial sobre las líneas A y R. Los riesgos relativos máximos se observaron entre las líneas LP y R (0.239), y entre LP y A (0.317). Esto significaba que en la fundación la probabilidad de muerte o eliminación asociada a una coneja LP era 0.239 o 0.317 la probabilidad asociada un animal A o R. Con respecto a las comparaciones en tiempos fijos, el patrón de las diferencias entre la línea de A y las otras líneas fue similar a los observados en la fundación. Aunque en general, con el progreso de la selección las diferencias entre las líneas tendieron a reducirse, esto era consecuencia del mayor efecto de la selección natural sobre las líneas de baja longevidad en su origen. Para las cuatro líneas maternales, se observó una gran similitud entre las diferencias observadas en los tiempos fijos, usando el modelo IM y las diferencias predichas usando el modelo CM, lo que es una indicación de que el modelo genético completo puede ser adecuado para analizar el conjunto de datos de estas poblaciones de conejos. Este no fue el caso para la línea paternal R, con la tasa más baja de censura, y con unas características reproductivas y de crecimiento muy diferentes a las de las otras líneas maternales. En base a los resultados observados en este capítulo se puede afirmar que en cuanto a longevidad, no parece acertado como criterio para fundar nuevas poblaciones atender exclusivamente a que una cierta población satisfaga los estándares morfológicos de una raza determinada, en el caso de la línea A el estándar de la raza Neozelandés blanco. Sin embargo, considerar directamente un carácter que se quiera potenciar, como es el caso de la longevidad en la línea LP, y elegir animales extremos para ese carácter sí parece más razonable para aumentar la media de este carácter en la población base.

RESUM

L'objectiu global de la present tesi va ser estudiar la longevitat funcional en cinc línies espanyoles de conills, el caràcter es va definir com la longitud de la vida productiva (LPL). Quatre de les línies estudiades van ser maternals (A, V, H i LP) fundades per diferents criteris, però totes elles seleccionades per grandària de ventrada al deslletament. La quinta va ser la línia paternal R, fundada i seleccionada per creixement diari post-deslletament entre els 28-63 dies. Aquestes línies s'han desenvolupat a un nucli de selecció situat en les instal·lacions del Departament de Ciència Animal de la Universitat Politècnica de València. Les dades utilitzades van ser arreplegades durant els programes de selecció des de la fundació fins a la 44ª, 39ª, 10ª, 8ª i 32ª generació de selecció per a les línies A, V, H, LP i R, respectivament. Per a una adequada avaluació genètica dels animals en el nucli, alguns criteris d'eliminació que s'utilitzen habitualment en les granges comercials nos es varen emprar; es a dir, les conilles amb nivells baixos de producció, baixa prolificitat o amb cert retard reproductiu no s'eliminen D'aquesta forma, la LPL de la conilla va reflectir directament la seua longevitat funcional.

Al Capítol 3, dirigit a comprovar l'heterogeneïtat genètica de la longevitat entre les 5 línies, es van estimar les variàncies additives i les seues corresponents heretabilitats efectives. A més a més, es va avaluar la importància de factors dependents del temps, com l'orde de la palpació positiva (OPP) , l'estat fisiològic (PS) i el nombre de llorigons nascuts vius (NBA) sobre el determinisme genètic de la longevitat. Per a això es van utilitzar 4 models de Cox de riscos proporcionals; el primer model (Model 1) va incloure tots els factors anteriorment assenyalats, a més de l'efecte de l'any-estació, l'efecte de la consanguinitat i, finalment, el valor additiu dels animals com a efecte aleatori. Els altres tres models van ser igual que el Model 1 però excloent l'OPP (Model 2) , o PS (Model 3) , o NBA (Model 4) . Les dades de longevitat estaven referides a 15,670 conilles i van tindre una taxa de censura de 35.6%. La genealogia completa va involucrar a 19,405 animals. Es van realitzar anàlisi tant de cada línia per separat com del conjunt de totes les línies utilitzant els 4 models. A l'anàlisi conjunta es va substituir l'any-estació per la combinació línia-any-estació. Les estimes d'heretabilitat efectiva (Model 1) per a la

longevitat en les 5 línies van ser baixes i van variar de 0.02±0.01 a 0.14±0.09, i en conseqüència, no es recomana incloure aquest tret com a criteri de selecció en els programes de millora de conill. A pesar de la gran variació de les estimes puntuals d'heretabilitat, els corresponents intervals $HPD_{95\%}$ sempre es van solapar i per tant la hipòtesi que totes les línies tinguen la mateixa heretabilitat no va poder descartar-se. Comparant les estimes de variància additiva dels 4 models, es va observar que l'exclusió de PS va incrementar la variància additiva, aproximadament, en un 51, 39, 38, 83 i 75% en les línies A, V, H, LP i R, respectivament. No obstant això, l'exclusió d'OPP o NBA no va conduir a canvis rellevants en les estimes de la variància additiva. Així, es pot concloure que part de les diferències genètiques de la longevitat podrien estar relacionades amb la forma en què la femella acumula risc pel fet que va passant d'un estat fisiològic a un altre i en el temps que passa en cada un d'a questos estats. És a dir que el patró de PS pel que passa cada femella al llarg de la seua vida tindria un cert determinisme genètic i que aquest està correlacionat amb el de la longevitat. Les tendències genètiques més pronunciades es van observar per a les línies A i H, en concordança amb el major paper que la selecció natural puga tindre sobre les línies de més baixa longevitat mitjana (línia A) i també en concordança amb les majors estimes d'heretabilitat observades (línia H) . El risc de mort o eliminació disminuïa a mesura que avançava l'OPP, observant-se el risc més alt durant els primers dos parts, en què les conilles encara estan creixent el que seria un factor de risc important. El nivell No-Gestant-No-Lactant de PS va tindre el major risc en comparació amb els altres nivells. Aquest nivell s'interpreta com indicador de baixa fertilitat i/o problemes de salut de la conilla. En relació als altres nivells de PS pareix que en general l'estat de lactació de les conilles (lactant o no lactant) té una major influència en la definició del risc a què estan sotmeses les conilles que el seu estat reproductiu (gestant, no gestant, desconegut) . Les conilles que tenien zero NBA van tindre el major risc de mort o eliminació, encara que per a la resta de nivells de NBA es va apreciar una disminució del risc a mesura que augmentà la prolificitat. En aquestes poblacions no es du a terme eliminació per producció per tant el major risc relacionat amb grandàries de ventrada baixos podria estar associat amb trastorns patològics subjacents. Cal assenyalar que, a la línia LP, la magnitud dels contrastos entre els diferents nivells d'OPP, PS i NBA va ser major que en les altres línies, la qual cosa pot ser considerat com un efecte d'escala a causa del criteri de fundació utilitzat en aquesta línia que va augmentar la seua longevitat i per tant també el rang dels factors que li afecten.

Al Capítol 4, es van estimar les correlacions genètiques i ambientals entre la longevitat i dos caràcters de prolificitat [nombre de llorigons nascuts vius (NBA) i el nombre de deslletats (NW)]. El fitxer de dades va incloure 58,329 parts i 57,927 deslletaments. També es van estimar les correlacions entre longevitat i el percentatge de dies que la conilla va passar en els diferents estats fisiològics respecte a la totalitat de la seua vida productiva. L'objectiu d'aquesta segona estimació de correlacions era el d'explicar els canvis observats en les estimes de la variància additiva de longevitat al eliminar del model el PS (Model 3 en Capítol 3). Respecte a les prolificitat les estimes d'heretabilitat van variar de 0.05±0.02 a 0.11±0.01 per al NBA i de 0.04±0.02 a 0.12±0.01 per al NW. En general aquestes estimes van ser baixes i van tendir a disminuir des del naixement fins el deslletament. Les estimes més baixes van ser en la línia H i açò pot ser conseqüència del criteri de fundació seguit en aquesta línia. L'única línia per a la que es pot dir que la correlació genètica entre NBA o NW i el risc va ser significativament diferent de zero va ser la línia LP. Per tant, la longevitat i la prolificitat no poden considerar-se com a objectius antagònics de selecció. Les estimes d'heretabilitat del percentatge de dies en cada estat fisiològic van ser baixes i van variar de 0.02±0.02 a 0.11±0.05, 0.01±0.03 a 0.06±0.03, 0.01±0.01 a 0.10±0.03, 0.03±0.02 a 0.10±0.09, 0.06±0.03 a 0.19±0.06 y de 0.01±0.03 a 0.11±0.03 per al percentatge de dies que la conilla va passar en els estats abans de la palpació/no lactant, gestant/no lactant, no gestant/lactant, abans de la palpació/lactant, gestant/lactant i no gestant/no lactant, respectivament. Quant a les correlacions entre longevitat i els percentatge de dies que la femella va passar en cada estat fisiològic, va haver-hi evidències de correlacions genètiques no menyspreables entre els dos caràcters, si bé els errors estàndards de les estimes no van permetre demostrar que aquestes correlacions foren significativament diferents de zero. Per tant, la hipòtesi plantejada al capítol 3 per a explicar els canvis observats en les estimes d'heretabilitat al no considerar el PS en el model no pot descartar-se.

Al Capítol 5 es compararen les longevitats mitges de les 5 línies en la seua fundació i en períodes de temps determinats durant el seu procés de selecció. Per a la comparació de les línies a l'origen, es van utilitzar totes les dades i un model genètic (CM) que incloïa els valors additius dels animals, per la qual cosa es va considerar l'efecte de la selecció a partir de la fundació. La comparació en temps fixos es va fer en períodes corresponents als 18 últims mesos en què almenys quatre línies compartien les mateixes condicions ambientals i de maneig (des de març de 1997 fins a setembre de 1998 (línies A, V, H i R) i des de març 2011 fins a setembre 2012 (línies A, V, LP i R)). En aquesta comparació es va utilitzar el mateix model que en l'anterior, però excloent els efectes additius del model d'anàlisi (IM) , utilitzant només les dades corresponents a cada període, per la qual cosa les diferències entre les línies incloïen els canvis deguts a la selecció. Les línies V, H i LP van mostrar una superioritat substancial sobre les línies A i R. Els riscos relatius màxims es van observar entre les línies LP i R (0.239) , i entre LP i A (0.317). Açò significava que en la fundació la probabilitat de mort o eliminació associada a una conilla LP era 0.239 o 0.317 la probabilitat associada un animal A o R. Respecte a les comparacions en temps fixos, el patró de les diferències entre la línia de A i les altres línies va ser semblant als observats en la fundació. Encara que en general, amb el progrés de la selecció les diferències entre les línies van tendir a reduir-se, açò és conseqüència del major efecte de la selecció natural sobre les línies de baixa longevitat en el seu origen. Per a les quatre línies maternals, es va observar una gran similitud entre les diferències observades en els temps fixos, usant el model IM i les diferències predites usant el model CM, la qual cosa és una indicació de que el model genètic complet pot ser adequat per a analitzar el conjunt de dades d'aquestes poblacions de conills. Aquest no va ser el cas per a la línia paternal R, amb la taxa més baixa de censura, i amb unes característiques reproductives i de creixement molt diferents de les de les altres línies maternals. Basant-se en els resultats observats en aquest capítol es pot afirmar que en relació a longevitat, no pareix encertat com a criteri per a fundar noves poblacions atendre exclusivament a que una certa població satisfaça els estàndards morfològics d'una raça determinada, en el cas de la línia A l'estàndard de la raça Neozelandès Blanc. No obstant això, considerar directament un caràcter que es vullga potenciar, com és el cas de la longevitat en la línia LP, i triar animals extrems per a eixe caràcter sí que pareix més raonable per a augmentar la mitjana d'aquest caràcter a la població base.

Chapter 1

LITERATURE REVIEW

LITERATURE REVIEW

Longevity is a functional trait directly related to farm profitability. The species in which the breeders have paid more attention to longevity is the dairy cattle due to its relative economic values. Increasing longevity reduces costs associated with rising or purchasing replacement females, an increase in the total milk production of the herd by increasing the proportion of mature animals with a greater production per lactation, increases the health and fitness of the animals, It also allows a reduction in health care costs, especially those caused by mastitis (Tempelman, 1998; Vukasinovic et al., 2001).

To establish a successful industry breeding program to improve functional traits (the term functional traits is used for those characters of an animal which increase efficiency not by higher output of products but by reduced costs of production) there are several prerequisites: there needs to be a well-defined and measurable trait that will indicate good animal function, the indicator trait must have a genetic component of variation, and be genetically correlated with the trait of economic importance in the breeding objective (Eady and Garreau, 2007). The relative economic importance of longevity in rabbits will be discussed.

In rabbit breeding programs, selection in maternal lines is mainly focused on litter size at birth or at weaning, and in paternal lines on feed conversion, indirectly selected through daily gain (Baselga and Blasco 1989). Recently, other traits such as longevity have been considered in selection objectives (Garreau et al., 2001; Sánchez et al., 2004) although it is difficult to improve this trait through conventional breeding methods because of the low heritability, the time needed to obtain relevant information and the complexity of the methods used to statistically analyse this trait. However, in mice, it has been clearly demonstrated that it is possible to improve reproductive life and number of parities by selection on phenotypic performances (Farid et al., 2002). Using longevity as foundation or selection criterion of rabbit lines will be presented.

One of the objectives of any program of selection in rabbits is to offer highly productive does to the breeders and at the same time these does should have a high production lifetime that mean resistance against diseases and low replacement rates. In this respect, different genetic groups can have different longevities and productive potentialities, and in this way has interest the comparison between breeds and lines of rabbits to know the differences in longevity and other productive traits, and in the genetic determinism of those traits as well. So, the genetic variability of longevity between and within rabbit populations will be commented.

Intensive meat rabbit production is based on the three-way crossbreeding scheme, which mainly uses crossbred does, coming from the cross of two maternal lines (Baselga et al., 2004). The length of productive life of the crossbred does will depend on both the longevity of the maternal lines involved in the cross and on heterotic effects that might appear. Consequently, it is important to compare the longevity of lines involved in the cross, and determine the genetic variability within each line to check the possibility of including longevity as one of the selection objectives in these lines. A detailed discussion concerning the foundation and selection procedures of maternal and paternal lines, accompanied by a list of some new lines for meat production will be presented.

In this context, the maternal lines developed at the nucleus of selection of the Animal Science Department, Universidad Politécnica de Valencia (UPV) founded on different criteria and being selected for litter size at weaning, together with the paternal line, which is usually used as a terminal sire in the three-way crossbreeding scheme, are considered a convenient animal material to study the genetic determinism of the longevity, as well the systematic factors affecting the trait, the genetic and environmental association between prolificacy and longevity in these lines, and the consequences of the current programs of selection on the longevity of the does.

Later, it will be presented a historical review of the methods used to analyse longevity more focused on the survival analysis methodology because it is the most frequently used.

1.1 Rabbit lines for meat production: Foundation and selection processes

Intensive meat rabbit production is based on the use of maternal and paternal lines which had been founded depending on different criteria. One common criterion is based on the concept of breed, in which the founder animals should maintain the standard morphological characteristics of the breed to which the animals belonged that after two or three generations of inter-se mating gives rise to the new line (Baselga, 2004). Other criteria are more concentrated on the economically important traits. One way to do it is attempting to find two or three populations, no matter their genetic origin that are clearly outstanding for the traits important to the desired specialisation of the line.

Furthermore, these populations should be mated during two or three generations without selection to obtain the new synthetic specialised line. Another procedure relies on applying very high intensities of selection for the traits of interest in very large populations such as the commercial populations. This method has been found successful in pig breeding programs (Bidanel et al., 1994). The criterion based on the concept of breed may be accompanied by some problems. One problem comes if the sampled populations are genetically poor for the traits of interest and consequently the starting point for the new line will be low. Another problem could be health issues that could appear when all the founder animals came from different and relatively numerous farms are put together in the same rabbitry (Baselga, 2004). After the foundation of the new line, the breeder will have to define the selection objectives; this decision will depend on the economic weight of the traits, their heritability, their variability and the genetic association between them and other economic traits (Falconer and Mackay, 1996). These foundation approaches, above commented, may have some consequences on the genetic improvement of the rabbit lines during their selection processes and also may determine the possibility of using them in a crossbreeding program. Unfortunately, the studies concerned with examining the effects of foundation criteria on the productive traits of maternal rabbit lines are very scarce. To my knowledge, there are only two works that studied the consequences of using different foundation criteria in four maternal rabbit lines which are selected for litter size at weaning (Ragab and Baselga, 2011) dealt with doe and litter traits, and Mínguez et al., (2015) in the same lines but concerned with growth traits.

Diversity of rabbit breeds and lines offers the opportunity to increase the efficiency of meat production. Therefore, creating new lines of rabbits could be of interest in order to increase performance of crossbred does; these does are considered as the backbone of the commercial rabbit production, whereas the intensive meat rabbit production is based on a three-way crossbreeding scheme (Figure 1). This scheme is also used in the production of other prolific livestock like pigs. A first cross involves two maternal lines; these lines are created and reared in the selection nucleus, and commonly selected for litter size to produce crossbred does (this step is performed in multiplier farms). Sometimes, this step is conducted in the commercial farms considering that in this case the does will be more adapted to the environmental and managerial of the farm in which they will produce. However, this procedure has the inconvenient of it is required to keep a number of cages for the females producing crossbreds. A second cross consists on mating males of a third line which it is known as terminal sire, featuring fast growth rate and good feed efficiency, with the crossbred does to produce the rabbits to be slaughtered for meat (this step is performed in commercial farms).

The aim of the cross between the maternal lines is to take advantage of the expected positive heterosis in reproductive traits, the eventual complementarity among the lines and the dissipation of the inbreeding accumulated within the lines (Baselga, 2004). As the selection usually is done within lines, it is expected that the heterosis will be maintained along the generations of selection and that the genetic progress obtained selecting the maternal lines will be capitalised on top of the heterosis and expressed in the crossbred does (Baselga et al., 2003). Moreover, the cost of the crossbred does is relatively lower than the purebred does due to the costs accompanying the selection and maintenance of productive animals. The method requires a scheme, based on the maintenance and selection of the pure stocks and the multiplication and diffusion of the crossbred does.

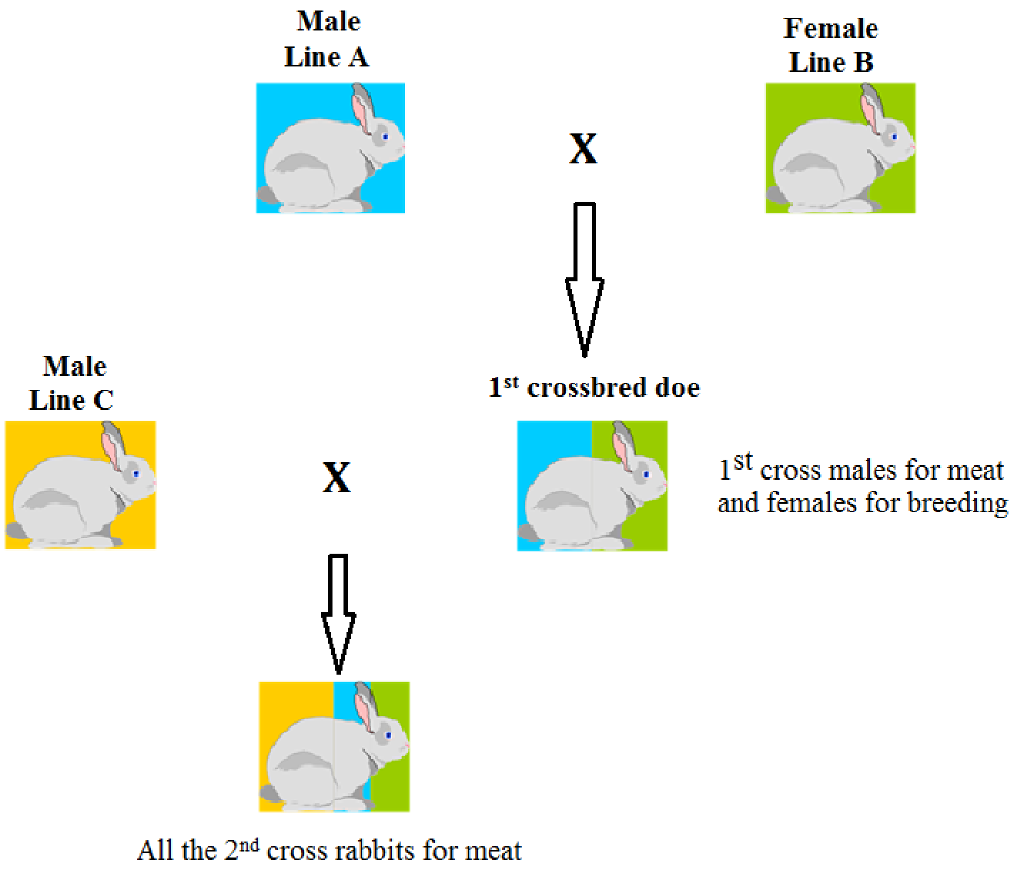

Figure 1 Three-way cross scheme in rabbits (lines A and B are maternal lines while C is paternal line).

1.1.1 Maternal rabbit lines

The foundation and development of specialised lines is a crucial activity due to the high requirements, organisation, experience and money needed. The lines are maintained as closed populations and the productive lives of their animals in the nucleus are shorter and the overall yield lower (the females are removed between the 4th and 6th parities) than the commercial does. Also, it is necessary a network for the distribution and sale of animals. So, in countries where the rabbit industry has not yet reached a proper level of organisation, it may not be convenient to select sire and dam lines for a subsequent crossbreeding program (Garreau et al., 2004). An alternative could be the development of multipurpose lines, through simultaneous selection for litter size and growth traits (Moura et al., 2001).

Selection methods to develop new synthetic lines of rabbits are more complicated for maternal lines than for paternal lines. This complexity is due to the fact that litter size traits are not expressed in both sexes and to the low values of heritabilities for reproductive traits (Baselga, 2004). Thus, during the genetic evaluation of does and bucks it is necessary to consider as many individual and relative records as possible. As consequence of the information accumulation, the generation interval for selection in maternal lines is longer than in selection of paternal lines, and consequently, it could be necessary to take into account some environmental and physiological effects in the evaluation models (Baselga and García, 2002). However, family index including the own information and information of the relatives were proposed to carry out such genetic evaluation (Baselga et al., 1984), and seem to provide good results. But currently, mixed model methodology (BLUP) is the most common procedure used in evaluation. One of the biggest differences with family index is that some environmental and physiological effects are considered in the model.

The most common direct criteria used in selection programs of maternal lines is litter size at birth or at weaning (Estany et al., 1989; Gómez et al., 1996; Rochambeau et al., 1998; Baselga and García, 2002). Despite the heritability of litter size at weaning is lower than the heritability of litter size at birth (Piles et al., 2006c); most of maternal lines are selected by litter size at weaning, since this trait reflects both the prolificacy as well as the milking and maternal ability of the doe. In some cases the criteria included litter size at birth and weight at nine weeks to prevent negative responses in adult weight (Bolet and Saleil, 2002), number of teats (Rochambeau et al., 1988). In other cases selection programs were practiced for traits related with the ability of the doe for lactating and nourishing the progeny, such as weight at weaning (Garreau and Rochambeau, 2003). Selection for ovulation rate and uterine capacity has been successfully performed as indirect ways for improving prenatal survival and litter size in rabbits (Ibáñez-Escriche et al., 2004; Mocé et al., 2005; Santacreu et al., 2005; Laborda et al., 2011). In addition, reducing the heterogeneity of the rabbit birth weight within litters might be useful in selection programs (Bolet et al., 2007). Litter size at 63 d or at the slaughter age is a relevant criterion of selection from the viewpoint of the breeder, but considering this trait implies large generation intervals, and the interference of the mortality of rabbits till this age that is more affected by the environmental effects than by the effects of the doe (García et al., 1982). Selection for hyperprolificacy in commercial rabbit populations using high intensities of selection has been a successful way to establish maternal rabbit lines (Cifre et al., 1998). By the same way, selection for hyperlongevity seems to be a good criterion to create new lines of rabbits (Sánchez et al., 2008). The response due to selection in maternal lines ranged between 0.05-0.13 kits born alive or weaned per litter and generation (Baselga, 2004).

The Spanish long-lived-productive line (LP) founded on hyperlongevity and being selected for litter size at weaning is a good example of the success of the foundation process. Its foundation criterion seems to have had interesting consequences on some productive and reproductive traits. Comparing the LP and V lines, Theilgaard et al. (2009) reported that LP does had a later reproductive senescence, and a greater adaptability to maintain the productive level in the face of nutritional limitations than line V. They attributed the superiority of LP does to the use of their body reserves giving priority to the maintenance of a high level of reproduction. By the contrary, the line V gave priority to the maintenance of the body condition but the reproduction was affected. Similarly to these findings, Friggens et al. (2012) reported in dairy cows that the way in which such animals allocate their resources to different life functions, is a major factor in their robustness. Also, Ferrian et al. (2013) observed a better immunological response of LP female rabbits to a lipopolysaccharide challenge. In addition, Savietto et al. (2013) in a comparative study between V and LP lines under different environmental and nutritional conditions, found that LP does faced better the opposite challenges such as the high environmental temperature (HC) and low-energy fibrous diet (NF). The total number of kits born of LP does was not affected by the NF environment, while the V does had -1.78 kits less than those reared in a normal environment. Furthermore, the milk yield of LP does was higher than V does not only in the normal environment but also in the HC and NF environments. They added that LP does use directly the digestible energy for reproduction with little change in the perirenal fat thickness (PFT), whereas V does actively use the PFT reserves for reproduction. The robustness and the high ability to withstand environmental and productive challenges of the LP does could be considered as a consequence of the foundation criteria used to create this line, the founder does must had a good long-term capacity to face the seasonal and punctual fluctuations in the environmental conditions that occurred in commercial farms from which they came. All these studies demonstrate the robustness of the LP line and its possible higher adequacy for rabbit meat production in hot climate countries and/or feed deficiency.

All-over the world, the oldest program for rabbit breeding and improvement is the French program that was started in 1969 by French National Institute for Agricultural Research "INRA" (SAGA, Toulouse), its objective was to produce paternal and maternal lines of rabbits (Rouvier, 1981), and followed by the Spanish program that started in 1976. The maternal line, INRA2066, selected for litter size at birth, and the INRA1077, selected initially for litter size at weaning, are crossed to produce the crossbred doe INRA1077 × INRA2066 (Rochambeau, 1998; Garreau et al., 2004). A new selection experiment was started in 2003 to develop the line INRA1777 through selection for litter size at birth, together with individual weaning weight (Garreau and Rochambeau, 2003); longevity was added later as a new criterion of selection (Garreau et al., 2001 and 2004). A divergent selection experiment was carried out on INRA1077 line using the functional longevity as a criterion of selection based on the genetic merit (Garreau et al., 2008; Larzul et al., 2014). In commercial farms, these French lines are genetically improved by some companies such as Hypharm (www.hypharm.fr) to create new synthetic paternal and maternal lines for meat production (hyplus, hycole, ..,etc) to be distributed within France and other European countries.

In Spain, long-term selection experiments were carried out to produce synthetic lines to be used at commercial farms. The two public centres that joint their efforts in developing a program of rabbit genetic improvement are the Department of Animal Science (UPV, Valencia) and the Rabbit Science Unit (IRTA, Barcelona). In IRTA, it was developed a maternal line named Prat, founded in 1992 from a closed population with 178 crossbred animals (146 females and 32 males), after two discrete generations without selection. Selection was practiced for litter size at weaning using a BLUP under a repeatability animal model. The UPV nucleus of selection has developed four maternal lines (A, V, H and LP). These lines are the animal material used in the present thesis and for this reason their foundation and selection histories will be discussed later. The French and Spanish breeding programs have kept their work uninterrupted until now and all the lines created at the beginning have undergone more than forty generations of selection.

Other short experiments were realised in other countries in order to develop new specialised or multi-purpose rabbit lines. In Brazil, a multi-purpose line named Botucatu was selected for litter size at weaning and post-weaning growth rate by independent culling levels (Moura et al., 2001). The multi-purpose index used in that experiment is no longer used for the creation of other lines. In Saudi Arabia, line V rabbits were imported in the year 2000 and were crossed with one desert Saudi breed (Saudi Gabali; S). There was some evidence that line V rabbits and their crosses could produce efficiently under hot climate conditions (Khalil et al., 2002 and AL-Sobayil and Khalil 2002). From this program, two synthetic lines; Saudi-2 as a maternal line with the structure $((\frac{3}{4}V\frac{1}{4}S)^2)^2$ and Saudi-3 as a paternal line with the structure $((\frac{3}{4}S\frac{1}{4}V)^2)^2$ were developed from crossing Saudi Gabali and line V rabbits, both lines are selected for litter weight and individual weight at 84d.

In Egypt, great efforts have been made since 1998 to select for one exotic maternal line under local conditions and to develop and select local lines based partially on local breeds. The first line was developed from crossing Baladi Red with line V and this line, named APRI, was selected for litter weight at weaning (Youssef et al., 2008). In March 2003, a selection program was started to produce a synthetic multi-purpose line named Moshtohor resulting from crossing Sinai Gabali with line V and selected for litter weight at weaning and live weight at 56 d (Iraqi et al., 2008). In Uruguay there are two lines selected for litter size at weaning, the first one is a New Zealand White and the second is a duplicate of the line V (Capra et al., 2000 and García et al., 2000). A brief description of rabbit lines developed in different countries is shown in Table I.1.

1.1.2 Paternal rabbit lines

The selection of paternal rabbit lines has the objective of improving the feed efficiency rate of the animals that will be used later in subsequent three-way cross scheme as terminal sires. The most common criterion of selection in these lines is the postweaning daily gain (from weaning to slaughtering). This trait is easy to record and has a negative favourable genetic correlation with feed conversion index (Moura et al., 1997 and Piles et al., 2004). Whereas, Baselga (2004) reported that feed conversion index is not used directly in rabbit selection because it is expensive to record and would need electronic devices to enable recording of individual feed intake. Since the feed conversion ratio (FCR) has a high economic value in rabbit production, because achieve low values of this ratio means lower production costs and consequently increase the global profit (Armero and Blasco, 1992; Cartuche et al., 2014). Considering that feeding costs represent about 70% of the rabbit meat production costs. The postweaning growth is a heritable trait, its heritability ranged from 0.13 to 0.48 (Rochambeau et al., 1989; McNitt and Lukefahr, 1996; Moura et al., 1997; García and Baselga 2002; Piles et al., 2004; Mínguez et al., 2015). In addition, this trait is less affected to common litter effects than the individual weights at specific ages (Estany et al., 1992; Khalil and Al-Saef, 2008). So, this trait could be improved through individual mass selection which is the simplest and easier way to improve such heritable traits expressed in both sexes. Garreau et al. (2013) reported that direct selection for feed efficiency is recently applied in the French rabbit breeder Hypharm.

The response due to selection in paternal lines range between 18 and 35 g/generation for weight at market time and between 0.45-1.23 g/d.generation for daily gain (Rochambeau et al., 1994; Baselga, 2004), with correlated responses increasing adult weight, intestinal content and feed intake but decreasing feed conversion, dressing percentage and maturity at a fixed weight. Piles et al. (2004) reported that the selection for growth rate was associated with decrease in feed conversion ratio, but may have also been associated with decrease in carcass and meat quality. Selection for litter size at weaning seems to have a correlated response in growth traits, Quevedo et al. (2005) reported that selection litter size at weaning resulted in a decrease in individual weight at weaning, although the total litter weight at weaning increased. For this reason, in some maternal lines such as INRA1777, the individual weight at weaning is considered jointly with litter size at birth as selection criteria (Garreau and Rochambeau, 2003).

Other selection criteria used in paternal lines are those related to the slaughter and carcass traits. Some methods were used to improve carcass traits using computer tomography (CT-based selection) on the *longissimus dorsi* to indirectly select for dressing out percentage by determining the slaughter value of the animals *in vivo* (Szendrö et al., 1988; Nagy et al., 2006). The problem of this method is the high costs and the long generation intervals. Recently, residual feed intake under *ad libitum* feeding was investigated experimentally as a direct way to improve the feed conversion index (Larzul and Rochambeau, 2005; Drouilhet et al., 2013). Other criteria related to the production of semen or characteristics of the adult bucks could be used in the future as criteria of selection in the lines highly selected for growth (Piles et al., 2013).

Table I. 1 Maternal and paternal lines of rabbits for meat production.

Name of the line	Country	Origin of the line	Selection criteria	Reference
INRA1077	France	NZW & BW	LSB & 63d weight	Bolet and Saleil, 2002a
INRA1777	France	Line 1077	LSB & WW	Garreau and Rochambeau, 2003
INRA2066	France	CAL & GH	LSB	Brun, 1993
INRA2666	France	Line 2066 & Line V	LSW	Brun et al., 1998
INRA9077	France	NZW & BW	LSB	Bolet and Saleil, 2002b
Line A	Spain	NZW	LSW	Estany et al., 1989
Line V	Spain	Four specialised maternal lines	LSW	Estany et al., 1989
Line H	Spain	Hyperprolific commercial does	LSW	Cifre et al., 1998
Line LP	Spain	Long-lived commercial does	LSW	Sánchez et al., 2008
Line Prat	Spain	Crossbreds	LSW	Gómez et al., 1996
APRI	Egypt	Baladi Red & Line V	LWW	Abou Khadiga et al., 2012
Alexandria	Egypt	Baladi Black & Line V	Postweaning daily gain	Youssef et al., 2008
Moshtohor	Egypt	Sinai Gabali & Line V	LWW & 56d weight	Iraqi et al., 2008
Saudi-3	Saudi Arabia	Saudi Gabali & Line V	LWW & 84d weight	Youssef et al., 2008
Altex	USA	¼ CAL & ¼CHA & ½FG	Individual weight at 70d	Lukefahr, 1996
Botucatu	Brazil	Norfolk line	LSW & daily gain	Moura et al., 2001
Uruguay-V	Uruguay	Line V	LSW	Capra et al., 2000
Line R	Spain	Two paternal lines	Postweaning daily gain	Estany et al., 1992
Line Caldes	Spain	Crossbreds	Postweaning daily gain	Gómez et al., 1999
Pannon White	Hungary	NZW & CAL	Postweaning daily gain	Matics et al., 2014
Pannon Ka	Hungary	Crossbreds & Pannon White	NBA	Matics et al., 2014
Line L	Hungary	Crossbreds & Pannon White	Postweaning daily gain	Matics et al., 2014

NZW: New Zealand White; BW: Bouscat White; SR: Small Russian; D: Dutch; CAL: Californian; GH: Giant Himalayan; CHA: Champagne; FG: Flemish Giant; LSB: litter size at birth; LWB: litter weight at birth; LSW: litter size at weaning; WW: individual weaning weight; LWW: litter weight at weaning; NBA: number of kits born alive.

1.2 Longevity in rabbits

Functional traits refer to traits that increase the economic efficiency by reducing costs instead of increasing the quantity of saleable products. Longevity as a functional trait, in farm animals has had a lower attention in their breeding programs compared to the other economically relevant traits. It may be due to the complex methods used to study it. In rabbits, the study of longevity needs to have a reasonable database which requires a long time to collect data and consequently lengths the generation intervals.

Longevity as a functional trait is associated with productive life and therefore is important for economic, welfare and ethical reasons. In general replacement costs in animal production represent a more or less high component of production costs, depending on the species, especially when culling is involuntary (e.g., due to death or fertility problems). Therefore animal scientists are often studying ways to increase the average length of productive life of domestic farm animals or to decrease the frequency of involuntary culling. For the case of rabbit for meat production, the replacement rate is about 112% yearly (Prieto et al., 2014) with about 50% of the dead or culled does replaced during their first 3 parities (Rosell, 2003). The average pregnancy rate in the Spanish commercial farms is about 78.2% and the average number of parities per doe 5.7 (personal communication with bdcuni “database of technical management in Spanish rabbit sector”). In France, this replacement rate is about 115% and this rate is partly explained by the mortality of the does that is around 30% on average (Garreau et al., 2008).

The main problems associated with this high replacement rate are the replacement cost of the does, the greater frequency of less mature females (young does are still growing and are less immunologically mature at parturition, showing lower litter size and more health problems), and sometimes the management and pathological problems related to introduction of animals from other farms (Piles et al., 2006b). Moreover, from an animal falls sick until it is completely eliminated from the rabbitry passes a period in which the breeder has maintained an unproductive animal, this mean more costs. Therefore selective breeding to increase the length of productive life could be an alternative to reduce costs attributed to replacements and then increase the profitability of rabbit does. In addition, increasing longevity of the does means higher number of litters during the whole life, and spread the doe costs over a longer period of time and over a greater number of kits produced. Armero and Blasco (1992) stated that a 1% decline in the annual replacement rate is an increase in year profits of 0.34 € per doe. Cartuche et al. (2014) reported that longevity has low importance in the profit function in comparison with other productive traits, since all costs placed on reproductive stock are divided by the number of rabbits produced, according to their results, all costs on the doe should be divided by 44 kits (5.7 parities per doe multiplied by 7.7 rabbits sold per parity). However, they found that replacement costs and feeding the replaced doe account for 7.4% of the total costs of production. Their results were in accordance with those of Eady and Garreau (2007) who found that the relative economic value for functional traits were lower than those for production traits.

Despite the low economic weight of longevity in rabbits compared to other traits, considering other implications commented before, the importance of longevity may be increased. Even small changes in the longevity of a population under production could have remarkable economic, welfare and ethics consequences.

1.2.1 Functional and true longevity

There is a serious difference between voluntary and involuntary disposal concerning the interpretation of several longevity measurements (Miller at al., 1967). The culling in farm animals can be divided into two groups, the first group is the culling for voluntary reasons such as low productivity or selling and the second group is the culling for involuntary reasons like death, fertility problems and disease occurrence. This problem is discussed in some details by Ducrocq (1987), who proposed a clear distinction between true and functional stayability of dairy cows. True stayability is defined as the ability to delay culling and functional stayability is defined as the ability to delay involuntary disposal. According to this definition, functional rather than true stayability is the trait which should be selected for. These definitions are still subjective since a culling for low milk production or low prolificacy, for example, is in fact imposed by the economic environment and would not be eagerly sought by the farmer. Van der Linde et al. (2007) distinguished between the two types of longevity calling the longevity adjusted for voluntary culling as functional longevity and the longevity not adjusted for voluntary culling as productive longevity. Functional longevity can be considered as trait reflecting animal capabilities to skip involuntary culling, which gives a measure of vitality, health status and reproductive performance (Ducrocq, 1987; Dekkers, 1993). The studies concerning longevity of the rabbit does are very scarce. These studies were performed using data from selection nucleus, in which some common culling criteria in commercial farms were not considered, i.e. does with low levels of production or no strong reproductive delay were not culled. For this reason, no correction for prolificacy was needed, and consequently the doe's length of productive life (LPL) reflected exactly the functional longevity. For more details about the different definition of rabbit longevity and cumulative production it can be seen in the literature by Garreau et al, (2001); Sánchez, (2006); Piles et al, (2006a&b); Sánchez et al, (2008) and Larzul et al, (2014).

1.2.2 Genetic variability of longevity in rabbits

Some studies in rabbit populations have considered the number of litters, the number of matings or the age at culling to estimate genetic parameters or compare different lines (Garreau et al., 2004). Relevant differences in direct genetic effects for functional longevity were found between maternal lines of rabbits selected for litter size at weaning (Piles et al., 2006a). Lukefahr and Hamilton (2000), in a longevity study to compare different genetic types involving New Zealand White, Californian, and crosses between these two breeds, reported the superiority of the New Zealand White and crossbred does with respect to the Californian does. Piles et al. (2006a) in an diallel cross involved three maternal lines of rabbits, A, V, and Prat, noticed that a purebred A doe was twice as likely to be replaced as a crossbred Prat x A doe and as a general pattern, the genetic type with the lowest relative risk were those in which the Prat line was involved; those were followed by types involving the V line and finally by those in which the line A participated. Another work involving Spanish maternal lines of rabbits is by Sánchez et al. (2008), this is an experiment conducted to compare the performance of the new LP line with that of another well-known and well-performing line, the line V, and to determine whether this new line could be considered as a candidate maternal line for inclusion in the current 3-way crossing production scheme. They reported that LP line had better longevity especially later in life, while V line had better early prolificacy. If both lines were compared during the whole studied period, a log-hazard of -0.28 was estimated in favour of line LP. Piles et al. (2006b) in a study for assessing doe longevity in two different lines of rabbits, found that the heritability estimates for longevity in Prat and A1077 lines were quite similar despite differences in breeding schemes, voluntary culling rules, definition of reproductive longevity and modelling of the baseline hazard function; these estimates were 0.158 and 0.172 for Prat and A1077 lines, respectively. Ragab (2012) in a complete diallel crossbreeding experiment involving four maternal rabbit lines compared the four purebred genetic groups and their twelve crosses in terms of functional longevity. It was shown that at the early productive cycles, the risk associated to purebreds is higher than the risk of crossbreds. The contrary happened at the late productive cycles (fifth or more).

Regarding the variability within population, a number of studies reporting genetic variances and heritabilities have been published, Table I.2 summarizes their results. From these studies it could be concluded that in general the estimates of heritability of longevity are ranged from low to moderate. This fact, as well as the long time needed for recording relevant information, that only will be obtained in females, and its relative economic importance, seems to prevent the inclusion of this trait as a selection objective in traditional rabbit programs. Concerning the work of Youssef et al. (2000), they used REML and estimated heritabilities of 0.08 and 0.13 for number of litters and length of productive life, respectively. In that work they used a linear mixed model ignoring the censored data considering them as complete data, in addition they used a sire model to infer the genetic variance. The problem of implementing the sire model in rabbit populations aiming to have an equivalent animal model with the principles of the infinitesimal genetic model, usually far from being fulfilled due to the peculiar family structure in rabbits. Garreau et al. (2001), using different models, obtained an estimate of 0.05 under the most realistic model. The main problem when comparing the different heritability estimates for longevity is the existence of various forms to present this parameter, this is a result of the nonlinearity nature of the models used when studying longevity records and consequently, it is no obvious what is the adequate definition of the heritability to be used.

Table I. 2 Reviewed estimates of variance components and heritability for doe rabbit longevity.

Reference	**Breed / Line**	σ^2_S	σ^2_A	h^2	**Method**
Youssef et al. (2000)	NZW	0.22	-	0.13	Linear model without censoring
Garreau et al. (2001)	A1077 line	0.01		0.05	Weibull model, discrete variable
Garreau et al. (2001)	A1077 line	0.03		0.10	Weibull model, continous variable
Garreau et al. (2001)	A1077 line	0.06		0.24	Weibull model, unrelated sires
Sánchez et al. (2004)	V-line	0.02	-	0.08	Cox model
Sánchez et al. (2006a)	V-line	-	0.18	0.15	Cox model
Sánchez et al. (2006b)	V-line	-	0.25	0.19	Cox model (with residual term)
Piles et al. (2006b)*	Prat line	-	0.19	0.16	Cox model
Piles et al. (2006b)*	Prat line	-	0.31	0.24	Cox model
Piles et al. (2006b)*	A1077 line	-	0.21	0.17	Cox model
Piles et al. (2006b)*	A1077 line	-	0.23	0.19	Cox model
Larzul et al. (2014)	A1077 line	0.05	-	0.16	Cox model

* In this work there were different models, thus there were various estimates of variance components and different heritabilities; σ^2_S: sire variance; σ^2_A: additive genetic variance.

1.2.3 Genetic association between longevity and other productive traits

For the knowledge of the genetic determinism of doe´s longevity it is important to properly know the genetic relationship with other traits, particularly with traits that are included in the selection objectives of breeding programs. In rabbits, the studies that focus on the estimation of the genetic relationship between longevity and other economically traits are scarce, since these studies require large datasets, like the ones resulted from long-term selection experiments which are already scarce. Rinaldo and Bolet (1988) showed that after seven generations of selection on litter size at weaning, neither the number of litter per doe nor the number of days of productive life were affected. Theilgaard et al. (2006) showed that in crossbred does selection on litter size at weaning during 12 generations did not affect longevity.

Sánchez et al. (2006a) found that the estimated genetic correlations between longevity and litter size traits (number born alive (BA) and litter size at weaning (NW)) were not significantly different from zero; these correlations were 0.16 and -0.17 between longevity, and BA and NW, respectively. The environmental correlation between longevity and NW was favourable and very close to zero, while between longevity and BA was significantly different from zero (-0.11±0.016) being the estimated value favourable but still very low. From this study we could conclude that genetically longevity and litter size are not antagonistic objectives in breeding programs.

In pigs, sow longevity is also favourably associated with reproductive traits including age at first farrowing, farrowing interval and weaning to oestrus interval (Tholen et al., 1996; Serenius and Stalder, 2004; Serenius et al., 2008), showing, as in rabbits, that longevity and intensification of reproduction are not antagonistic. In this respect, Tholen et al. (1996) reported that the genetic correlation between weaning to conception interval (WCI) or farrowing interval (FI) in the first reproductive cycle and stayability ranged between -0.24 and -0.54. They added that, the selection for short WCI following the first farrowing should have favourable for longevity in sows. Similarly and in the same breeds, Serenius and Stalder (2004) found a moderate negative genetic correlation (-0.40 and -0.43) between farrowing interval and length of productive life in the Finnish Landrace and Large White. These negative values were expected because the farrowing interval increases due to problems in rebreeding sows after weaning. Stalder et al. (2004) stated that reproductive failure is the predominant reason for early culling of young sows from commercial pork operations. The relationship between longevity and production traits and carcass composition are generally slightly unfavourable and the strength and sign of the relationship can vary depending on the population being evaluated (Tholen et al., 1996; López-Serrano et al., 2000; Serenius and Stalder, 2004). Relationship between length of productive life and backfat thickness in a Finnish Large White population was unfavourable, being 0.22 the estimate of their genetic correlation (Serenius and Stalder, 2004), whereas the same genetic correlation in a Finnish Landrace population was close to zero. Serenius et al. (2008) found that LPL was moderately associated with the number of piglets weaned at first farrowing and with the age at first farrowing (posterior means of the genetic correlation were -0.20 and 0.36, respectively).

In dairy cattle, the genetic correlation between longevity traits and milk yield ranged from -0.11 to 0.84, between longevity and fat yield ranged from -0.17 to 0.76, and between longevity and protein yield ranged from -0.12 to 0.81 (Short and Lawlor, 1992; Vollema and Groen 1997; Tsuruta et al., 2004; Sasaki, 2013).

1.2.4 Selection for longevity in rabbits

So far, several studies dealing with genetics of rabbit does longevity have been published, and some of them have been developed within the framework of projects with the final aim of improving doe longevity. In one hand the Animal Science Department of the UPV (Valencia, Spain) created a new line, named LP (Long-lived and Productive) (Sánchez, 2006 and Sánchez et al., 2008), that was founded following a scheme similar to that applied in the selection for hyper-prolificacy in pigs and rabbits. In this case the selection criteria were hyper-longevity, selecting does in commercial farms which showed an extremely high productive life (does had at least 25 parities), and an average life prolificacy equal or above the population average. In the foundation of this line, it was intended to apply a very high intensity of selection for longevity, approximately, between two and five does were selected per thousand of females screened at the commercial farms of Spain and Portugal. The does were inseminated with semen from bucks of line V, the second step tried to get sons of a new batch of LP does mated to the males got in the first step. Another set of 15 LP does was selected and housed in the same lazaretto than the previous batch. These does were inseminated with semen coming from the bucks obtained in the first step and a total of 17 males were got. These males were grandsons of 11 of the LP does of the first batch. In the third step, a total of 32 LP does were detected in 25 farms. These does were inseminated with semen coming from the 17 bucks obtained in the previous step. The offspring was the initial generation of the LP line. Recently, the 10th generation of selection has been achieved.

In the other hand, at INRA (France) a population belonged to INRA 1077 line was selected for longevity in a divergent selection experiment (Garreau, et al. 2008), using exclusively within line information, in this case the selection criterion was the number of AIs a female was subject to during its entire life, and only males, progeny tested by their daughters, were selected according to this criteria (48 males were progeny tested), females were randomly selected and the selection efficiency was estimated in the 2nd generation. Based on the estimated genetic merit for longevity of 10 daughters bred in two different farms, 5 bucks considered to have high longevity (HL) and 5 to have low longevity (LL) were selected to produce the next generation. The difference in longevity observed between the two lines was +0.75 AI (32 days). In the first farm, the differences were mainly due to culling reasons (26% in the LL line *vs.* 14% in the HL line) since the mortality percentage was similar in the two farms. In the second farm, mortality and culling were both higher in the LL line than in the HL (33 *vs.* 15% and 19 *vs.* 7%, respectively). However, there was no differences between the two lines in terms of reproduction traits recorded for each kindling (Larzul et al., 2014).

The UPV´s LP line was compared to another maternal line (V) and it showed a slightly better longevity, and slightly lower prolificacy. Considering both traits, no differences in cumulative production were observed, the same as in fertility. Regarding the selection experiment in France, also better longevity was observed in the selected population (0.8 parturitions more) with an almost null effect on prolificacy. In these two populations further studies has been conducted to assess the physiological basis of the longevity, and apparently the management of body reserves is a key issue for establishing their better longevity, particularly under unfavourable environmental conditions (LP line: Theilgaard et al. (2009) and Savietto et al. (2013); INRA line: Garreau et al., (2010)).

1.3 Survival analysis

Different methods have been used to analyse longevity data. These methods differ on the rigour of their approach and we can comment examples such as 1) Mixed linear models without taking into account the censored data. Youssef at al. (2000) estimated heritabilities for lifetime production and cumulative production traits of rabbits. They found that the estimates of heritability of the lifetime production traits ranged from 0.05 to 0.13. Another work in which linear models without censoring were used (Lukefahr and Hamilton, 2000) involved several genetic groups of rabbits that were compared for cumulative traits over one year and for survival throughout this period. 2) Repeated binary records, depending on whether an animal still alive and remains in the breeding herd or not (0 or 1) at different time periods defined by the users. In this case it has been shown that repeatability or random regression models can be used to analyse this type of data (Meuwissen et al., 2002; Veerkamp et al., 1999).

Another methodology for the study of longevity is the survival analysis, which is widely applied to the fields of epidemiology and animal breeding. Survival analysis is a statistical methodology originally developed for research in medicine and engineering, to study the time to an event of interest; when this event is the death or culling we are dealing with longevity. Survival analysis combines information both from uncensored (the animal was dead or culled) and censored (the animal is still alive or productive at the end of the experiment) records in a single analysis, this statistical technique enables a proper statistical treatment of censored records and also it accounts for the nonlinear characteristics of longevity records. The goal of survival analysis is to analyse positive measures describing in some sense the width of the interval between an origin point and an end point. Often, the end point corresponds to death or culling and the length from the origin to the end is measured in number of days, months or years, etc. The end point (generally called “failure”) may also correspond to the occurrence of any type of event (recovery from a disease or success after an insemination) and the time measure can be expressed in euros or dollars spent or earned, kilograms of milk produced, litters born, etc (Ducrocq, 1997).

Cox (1972) and Kalbfleisch and Prentice (2002) described the method of survival analysis, modelling the risk of failure instead of the actual longevity of an animal. It relies on the concept of hazard at a given time, the limiting probability of being culled among animals still alive at the specified time. The hazard can be modelled for all records, whether censored or not. Famula (1981) was the first author who proposed survival analysis as a method to analyse length of productive life in dairy cattle. Smith (1983) and Smith and Quaas (1984) used survival analysis techniques to estimate breeding values of sires based on the length of productive life of their daughters. The techniques were further developed and adjusted for large scale applications by Ducrocq (1994) and Ducrocq and Sölkner (1994).

The main difficulties of the survival analysis of longevity data which in gran part are related to the limitations of the analyses programs can be identified as: 1) Necessity of approximated and peculiar multivariate analysis to estimate the genetic and phenotypic correlations between longevity and linear traits of economic interest. This point is particularly important as most of the information during early life will come from predictor traits (Brotherstone et al., 1998); 2) Complexity of the proportional hazards models used in the analysis; 3) Generally only one genetic effect is fitted for each animal throughout its whole life, i.e. the culling probability of two contemporaries have a constant ratio during their life (this could be solved by using time-dependent-sire-effects; Veerkamp et al., 1999). Regarding this point Damgaard, (2006) proposed an extension model for the Cox proportional hazard model to allow for time varying genetic effects. Nevertheless, he attributed the application of the suggested extension model to the capacity of computer power, and added that these models would not be applicable to large scale genetic evaluations with large numbers of animals. However, statistical complexity and computational difficulties related to these methods have delayed the adoption of this methodology and different indirect approaches have been proposed (Strandberg and Sölkner, 1996).

With the presentation of the statistical package "Survival Kit" (Ducrocq and Sölkner, 1994), survival analysis applied to genetic improvement became the technique of choice for studying longevity data. This statistical package implements both fully parametric models and semi-parametric models, allowing for both modelling time-dependent variables and the development of stratified analyses. When the models are fixed, the estimation is carried out by maximum likelihood, while when the models are mixed (frailty) the estimation is carried out by a Bayesian approach based on a Laplace approximation of the marginal posterior density of the estimated parameters, allowing different types of distributions such as Gamma, Multivariate Normal and Normal as priors, which allows in the latter case include relationship matrices, the program also allows the correlated random effects (Mészáros et al., 2013). The Survival Kit has been updated continuously and used by many researchers and it can be freely found at http://www.nas.boku.ac.at/nuwi-survivalkit.html.

Survival analysis has been applied in the animal breeding context to estimate genetic parameters for longevity. Presently, it is the methodology applied for routine genetic evaluation for longevity in dairy cattle in many countries (Van der Linde and de Jong, 2003). As the Bayesian statistics develops, the survival analysis using Bayesian approaches progresses also. Korsgaard et al. (1998) developed a method of MCMC adapted to the analysis of longevity data using semiparametric models, this approximation allowed the inclusion of several random effects and the estimation of variance components associated with them. This approximation allowed reaching the full marginal distributions of the parameters of interest, but not allowed the inclusion of the time-dependent factors in the model of analysis; in addition the computation needs were very high. The same approximation was used by Sánchez et al. (2006b) to study the rabbit doe longevity using a semiparametric log-Normal animal frailty model, in that study the same approach presented by Korsgaard et al. (1998) was used but extended to account for time-dependent covariables.

Regarding the multivariate analysis, Ducrocq et al. (2001) proposed a two-step approach for multiple trait evaluation of functional and production traits. First, univariate analyses are performed for each trait to get the genetic variance and to compute pseudo-records and their associated weights. Pseudo-records here can be regarded as records corrected for environmental factors to more complex situations such as repeated records and nonlinear traits. Combining these pseudo records in a multiple trait animal model, fixing the genetic and residual variances, one can get the estimations of genetic and environmental correlations and the approximated expected breeding values (MT-BLUP) (Figure 2). Tarrés et al. (2006) reported that the two-step approach proposed by Ducrocq et al. (2001) is an operational tool that can be implemented in many situations where a multiple trait approach is desirable but not applicable, either because of the huge size of the datasets analysed or the complexity and heterogeneity of the models to be implemented. Tarrés et al. (2006) tested this approach via simulation and obtained unbiased results. Another procedure for the joint analysis between linear Gaussian trait and a survival trait is the bivariate quantitative genetic model proposed by Damgaard and Korsgaard (2006) assuming that the unobserved log-frailty of the survival trait and the linear trait followed a bivariate normal distribution and including a Gaussian residual within the Weibull distribution but obviating any residual with the extreme value distribution, the model parameters were inferred from a Bayesian analysis using Gibbs sampling. This model was tested using two simulation studies using sire and animal models and involving time-dependent covariates showed that the estimated marginal posterior distributions covered well the placed high density to the true parameter values used in the simulation of the data, which is an indication of the suitability of this proposed procedure for inferring additive genetic and environmental correlation between the two traits. A recursive model to analyse jointly linear and survival traits was suggested by Martínez Ávila and Garcia Cortés (2007) considering that the productive (linear) trait is dependent on the phenotype of the survival trait, this means that one source of variation is given by the inclusion of the phenotype of one trait in the description of the other trait and by this way the linear trait maintain its specific distribution. The goodness of that method was validated via simulation. The sequential threshold model (STM) described by Albert and Chib (2001) was used by González-Recio and Alenda (2007) to perform a bivariate analysis for one discrete-time survival trait and a Gaussian trait. This method has some advantages such as it can describe physiological or decision processes that occur in a sequential order, can incorporate time-dependent covariates and censoring, accounts for what occurred in the previous stages increasing reliability of estimates, does not need a two-step approach to model both traits jointly, in addition this method can be considered as a less computing demanding method compared to other two-step methods.

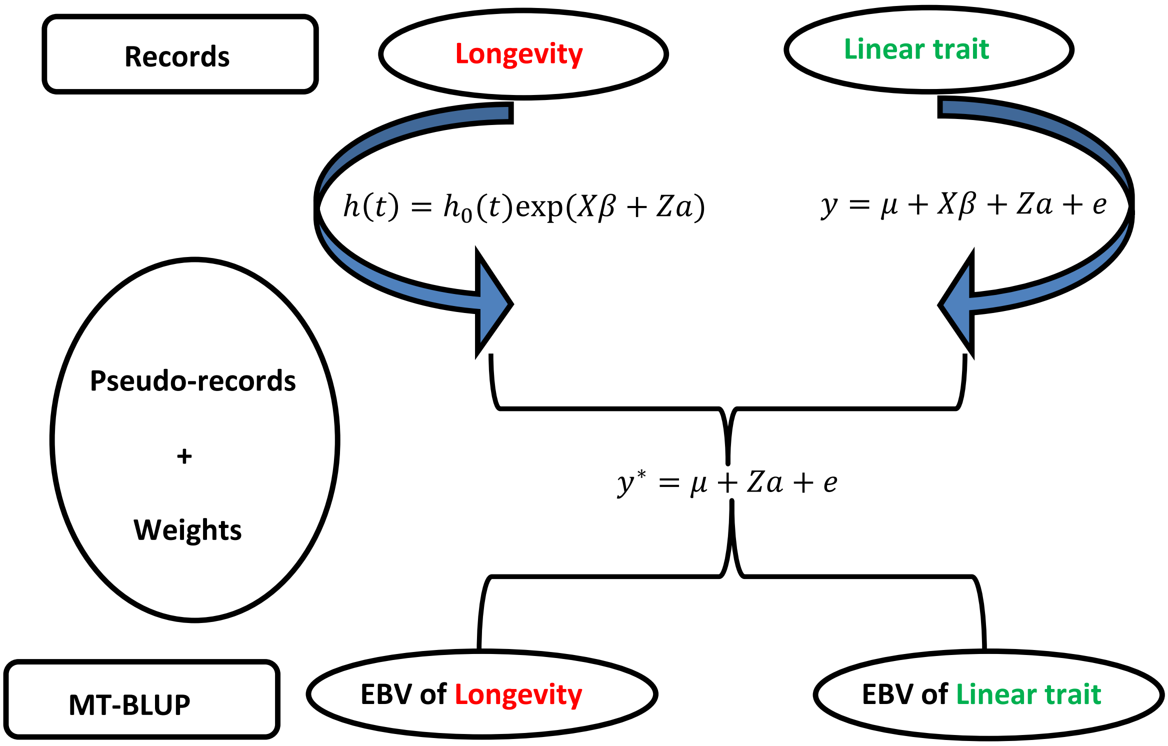

Figure 2 Scheme of the two-step approach for multiple trait evaluation of longevity (Non-linear trait) and a linear trait.

1.3.1 Description of longevity data and censoring

Studying longevity requires special statistical treatment for three main reasons: 1) the distribution of survival time is rarely known and in most cases, extremely skewed, thus methods based on assumption of normality have only limited use in the analysis of longevity data (Egger-Danner, 1993); 2) for part of the observations, only a lower bound of survival time is known e.g., for individuals still alive at the end of the study period. Several researchers tried to circumvent this problem by using indirect longevity indicators such as whether the cow is still alive at certain age (Everett et al., 1976) or lactation (Schaeffer and Burnside, 1974) or by replacing censored records by so-called projected records based on currently available information (Van Raden and Klaaskate, 1993); 3) the independent variables influencing survival time may themselves vary with time (e.g., current milk production, herd size, disease occurrence).

Longevity data can be defined using a set of functions of the time to the event of interest. The survival analysis techniques consist on fitting different models to these functions. Let T be the nonnegative random variable representing the failure time of an individual from a homogeneous population. T is assumed here to be continuous. The characteristics of T can be described through the following functions:

Survival function $S(t)=\Pr[T\geq t] = 1-\Pr[\mathrm{T}<t]=1-\mathrm{F(t)}$

Describe the probability that death occurs after time t, represents the fraction of individuals who are still alive at time t. Where F(t) is the usual cumulative distribution function of T.

Cumulative distribution function $F(t)=1-S(t)=\Pr[T<t]$

Is the complement of the survivor function, and therefore represents the fraction of dead individuals up to time t.

Density function f(t) = $\lim\limits_{\mathrm{dt}\to 0}\frac{\mathrm{Prob[t\leq T\leq t+dt]}}{\mathrm{dt}}$

$$=\frac{\mathrm{dF(t)}}{\mathrm{dt}}=-\frac{\mathrm{dS(t)}}{\mathrm{dt}}$$

The density function is the limiting probability that failure will occur between t and t + dt.

Hazard function h(t) = $\lim\limits_{\mathrm{dt}\to 0}\frac{\mathrm{Prob[t\leq T\leq t+dt|\ T\geq t]}}{\mathrm{dt}}$

$$=\frac{\mathrm{f(t)}}{\mathrm{S(t)}}=-\frac{\mathrm{d\log S(t)}}{\mathrm{dt}}$$

The hazard function is the limiting ratio of a probability over an interval length; this ratio is always positive and can be greater than 1. This function measures the risk of dying (failure rate) or being culled (culling rate). The hazard function h(t) specifies the instantaneous rate of failure at time t, conditional upon survival up to t. The hazard function is particularly useful in determining the appropriate failure distributions utilizing qualitative information about the mechanism of failure and for describing the way in which the chance of experiencing the event changes with time (Klein and Moeschberger, 2003).

Cumulative hazard function H(t) = $\int_0^{\mathrm{t}}\mathrm{h(u)du}\Longrightarrow\ \mathrm{S(t)}=\exp\ \{-\mathrm{H(t)}\}$

All these functions are linked, and thus, the knowledge of anyone of them implicitly defines the others. From the previous equations it could be concluded that the survival and hazard functions provide alternative but equivalent characterizations of the distribution of T. Given the survivor function, we can always differentiate to obtain the density and then calculate the hazard. Given the hazard, we can always integrate to obtain the cumulative hazard and then exponentiation to obtain the survivor function. The exact nature of f(t) or S(t) is not known but some information is available on how the failure rate will change with time.

Censoring is a phenomenon that implies certain proportion of incomplete observations, but the reason for this lack of information should be random, or independent of the event of interest. Censored data provide partial information in the sense that we only know that the event had not occurred when the records were obtained (Klein and Moeschberger, 2003); for this reason censored records should be included in the analysis because removing them or treating them as uncensored records could lead to biased estimates (Guo et al., 2001). Right censoring is the most important type of censoring in studies of LPL in animal production but there are other types. Right censoring can occur because an animal is removed before failure can be observed, or because the animal is subject to any factor that avoids observing the event of interest. Consequently, records of the eliminated animals for the end of generation of selection or if some animals are still alive when the analysis is performed should be treated as right-censored. In the case of studies involving functional longevity the event of interest will be death or culling because of involuntary reasons such as diseases occurrence.

For each animal i, there are a failure time Ti and a censoring time Ci but only one is observed. Ti for an uncensored observation (in this case, we know that censoring would have occurred after t = Ti and the censoring code = 1), Ci for a censored observation (in this case, we know that death would have occurred after t= Ci and the censoring code = 0). The main assumption in any survival analysis is the independence between the censoring and the event of interest (death or elimination). In other words, it is assumed that the censoring mechanics is independent when the rate of the occurrence of the event applied to individuals at risk in each time t > 0 is the same applied to censored individuals in case they were not censored (Kalbfleisch and Prentice, 2002; Martinussen and Scheike, 2006). A general assumption in all the survival analysis techniques is the randomness of the censoring mechanism, but sometimes this is not fulfilled, however it can be demonstrated that likelihood functions derived assuming random censoring still be useful if T variable (failure time) and C variable (censoring time) are independent.

1.3.2 Estimation of functions describing longevity data

1.3.2.1 Homogeneous populations

When all individual from a population are subject in a given time to the same risk, it is said that this an homogeneous populations, in this case the most relevant statistic would be just estimate of the aforementioned functions describing survival data, to accomplish this two alternative ways to describe such functions have been proposed, parametric and non-parametric models.

Parametric models

All the previous functions can be defined throughout a number of parametric models, the most commonly used are the Exponential and Weibull, but also Gamma, Generalized Gamma, Gompertz, Log-Logistic and Log-Normal could be used (Kalbfleisch and Prentice, 2002), and it would be needed to estimate the parameters of these models.

The hazard function determines which parametric model should be used. For example, If the hazard function it is assumed to stay constant over time $\{h(t) = \lambda = \text{constant}, \lambda > 0\}$ this means that the chances of failure at any time are the same regardless how long the subject has been on test (memoryless property). For this type of hazard function the parametric model to be used is the exponential in which the survivor function $S(t) = \exp\left(-\int_0^t h(u)du\right) = \exp(-\lambda t)$, and the density function is of the form $f(t) = h(t).S(t) = \lambda \exp(-\lambda t)$.

If the hazard functions is not constant, means that the chances of failure at any time are not the same. One of the most common parametric models is the Weibull distribution. The Weibull survivor function is a very simple modification of the exponential one, $S(t) = \exp\{-(\lambda t)^{\rho}\}$ where $\lambda > 0$ and $\rho > 0$ in this case, if $\rho = 1$ then S(t) reduces to the exponential survivor function, if $\rho > 1$ an increasing hazard is observed with time and if if $\rho < 1$ a decreased hazard is observed with time. The density function is of the form $f(t) = h(t).S(t) = \{\lambda\, \rho\, (\lambda t)^{\rho-1} \exp\,(-(\lambda t)^{\rho})\}$ in which the hazard function $h(t) = \lambda\rho(\lambda t)^{\rho-1}$. Thus, the Weibull model is more general and flexible than the exponential model that allows for hazard rates that are non-constant but monotonic. It is a two-parameter model (λ and ρ), where λ is the location parameter and ρ is the shape parameter because it determines whether the hazard is increasing, decreasing, or constant over time. Other parametric models would allow for non-monotonic hazard rates changes such as log-normal and log-logistic models, for more details regarding these models it can be seen at Kalbfleisch and Prentice, (2002) and Klein and Moeschberger (2003).

Non-Parametric models

Non parametric analysis allows the user to analyse data without assuming an underlying distribution, avoiding potentially large errors brought about by making incorrect assumptions about the distribution. On the other hand, the confidence bounds associated with non-parametric analysis are usually much wider than those calculated via parametric analysis, and predictions outside the range of the observations are not possible, furthermore, these types of analyses needs great computational requirements which limits their use. One of the most common non-parametric methods is the Kaplan-Meier estimator of the survivor function named as product limit estimator. A non-parametric estimate of the survivor curve S(t) can be obtained by describing the probabilistic definition of S(t) as a product of conditional probabilities:

$$\begin{aligned}\mathrm{S(t)} &= \mathrm{Prob}[\mathrm{T} \geq \mathrm{t}] \\ &= \mathrm{Prob}\left[\mathrm{T} > \mathrm{T}_{[1]}\right] \times \mathrm{Prob}\left[\mathrm{T} > \mathrm{T}_{[2]} \mid \mathrm{T} > \mathrm{T}_{[1]}\right] \ldots \\ &\times \mathrm{Prob}\left[\mathrm{T} > \mathrm{T}_{[k]} \mid \mathrm{T} > \mathrm{T}_{[k-1]}\right]\end{aligned}$$

where $\mathrm{T}_{[k]}$ is the largest observed failure time prior to t. A “natural estimator” of each conditional probability $\mathrm{Prob}\left[\mathrm{T} > \mathrm{T}_{[k]} \mid \mathrm{T} > \mathrm{T}_{[k-1]}\right]$ is: $\frac{\text{number still alive just after } \mathrm{T}_{[k]}}{\text{number still alive just prior to } \mathrm{T}_{[k]}} = \frac{\mathrm{n_k - d_k}}{\mathrm{n_k}}$. This natural estimator, combined with the probabilistic definition of S(t), leads to the following non-parametric estimator of the survivor curve: $\hat{\mathrm{S}}(\mathrm{t}) = \hat{\mathrm{S}}_{\mathrm{KM}}(\mathrm{t}) = \prod_{\mathrm{k}|\mathrm{T_k}<t}\left(\frac{\mathrm{n_k - d_k}}{\mathrm{n_k}}\right)$. This expression is known as the “product limit estimator of the survival function or Kaplan-Meier estimator” (Kaplan and Meier, 1958). It is also possible to

compute an estimate of the variance of $\hat{S}_{KM}(t)$ as $\widehat{Var}\left[\hat{S}_{KM}(t)\right] = \left[\hat{S}_{KM}(t)\right]^2 \sum_{k|T_k<t}\left(\frac{d_k}{n_k(n_k-d_k)}\right)$.

The Kaplan-Meier estimate of the survivor function $\hat{S}_{KM}(t)$ or the cumulative hazard function $\hat{H}(t)$ plays a key role when one wants to check whether a failure time variable follows a particular parametric distribution as a descriptive method of data in order to check the suitability of parametric models. The graphical test to check whether an exponential distribution fits the data will consist in a plot of: $-\log(\widehat{S}_{KM}(t))$ against t. If such a plot displays a straight line with slope λ and going through the origin, an exponential failure time distribution with constant hazard λ can be assumed. Similarly to the test of the suitability of the Weibull distribution, the plot of $\log\left[-\log\ \widehat{(S}_{KM}(t))\right]$ against $\log(t)$ should display a straight line with slope ρ and intercept $\rho\log\lambda$.

1.3.2.2 Heterogeneous populations

The models presented above deal with the data from homogeneous population. However, in most practical applications the population under study is not homogeneous. For example, individuals in animal breeding studies may differ in milk production, physiological status, and age at the first service. Maybe some of these covariates are of special interest, such as the effect of a treatment in a clinical trial, or they are nuisance parameters which influence the variable lifetime. The proportional hazard models are concerning with the analysis of data from heterogeneous populations, and account for this heterogeneity by allowing the fit of the different covariates which structure the population.

The proportional hazard models are the most common class of the survival models and may be seen as a type of regression models that use, to determine the functions previously mentioned, some explanatory variables (covariates) that could define sub-populations, for example different genetic groups. Many times we are more interested in how these explanatory factors affect the hazard than in how the hazard actually changes over time. Let $x = (x_1, \ldots\ldots, x_n)$, be a vector of covariates which affect the hazard through a vector $b = (b_1, \ldots\ldots, b_n)$ of regression variables. The hazard function of an individual with variables x could be written as $h(t, x) = h_0(t) * \exp(x^{\prime}\beta)$. The term $h_0(t)$ is called the baseline hazard function, i.e. the average hazard for the whole population. In this model, the ratio between the hazards of two individuals having covariates $\mathrm{x_a}$ and $\mathrm{x_b}$ is constant over time:

$$\frac{h(t,x_a)}{h(t,x_b)} = \frac{h_0(t)\exp(x'_a\beta)}{h_0(t)\exp(x'_b\beta)} = \exp[(x_a - x_b)'\beta].$$

This is why these models are called proportional hazard models. This has important consequences on the estimation procedures, which get simplified appealing to this property. The baseline hazard function can be modelled with different distributions for example Exponential or Weibull, depending on our assumptions regarding how the base hazard changes with time. However, the baseline can also be kept completely arbitrary as in the semi-parametric model, which is called the Cox model (Cox, 1972). Fitting the proportional hazard models includes the estimation of the unknown coefficients $\mathrm{b_1, b_2, \dots b_n}$ and, if a parametric form is assumed for the baseline, it is also needed to estimate the parameters describing this function. In the case of the Cox model as well as for any parametric model the vector b can be estimated with Maximum Likelihood. For the particular case of the Cox model a Partial Likelihood, Cox's Partial Likelihood is used, which is the part of the full likelihood that does not depend on the baseline hazard, thus not any parameter regarding the baseline will be considered during the estimation, but the baseline effect has been accounted for. Maximum Cox partial likelihood estimates have the same properties as those obtained working with true likelihood, e.g. are asymptotically unbiased and follow a multivariate normal distribution with variance-covariance matrix equal to minus the inverse of the Hessian of the log-partial likelihood function (Cox, 1975). This property is used to construct confidence interval and to perform hypothesis test regarding estimates of b.

As it has been mentioned, the proportionality between risks is an important feature, but there could exists situations when it is not fulfilled, one situation is when different baseline hazards function characterize different subsets of animals, and the other happens when during the life of an individual the values of some of its covariates change. Both situations can be accommodated in a straightforward way either in parametric regression models or in the Cox model by performing stratified analyses or by including time-dependent covariates (Ducrocq, 2001).

1.3.3 Frailty models in survival analysis

In most biological studies it is observed important biological variation between individuals that is taken into account by the inclusion of random effects linked to them (Scheike and Jansen, 1997). In survival analysis terminology the random effects are called frailty terms, which are unobserved random proportionality factors that modifies the hazard function of an individual, or of related individuals. The term frailty was introduced by Vaupel et al. (1979) in univariate survival models and the model was substantially promoted by its application to multivariate survival data in a seminal paper by Clayton (1978) (without using the notion "frailty") on chronic disease incidence in families. Proportional hazard models, whether they are parametric or not can be extended to include random effects. When the frailty term is defined separately for each individual the frailty component extracts part of the unobserved variation between individuals (Vaupel et al., 1979, Aalen, 1994, Damgaard et al., 2006) and therefore allows for a correction of the possible discrepancy between the variance of the observations and the one specified by the model. When the term of frailty is defined for a group of individuals, for example all daughters of a sire it describes the shared unobservable characteristics which act on the hazard of each member of the group (Anderson et al., 1992, Klein et al., 1992, Ducrocq, 2005).

The frailty terms can be included in $x'\beta$ and Bayesian approaches have been adopted for their prediction, regarding the distribution of the frailty terms as a prior assumption in the analysis. Frailty models provide an essential tool for animal breeders who care about prediction of random variables, i.e. breeding values. But for this prediction it is needed to know some parameters regarding the distribution of the frailty terms, in particular would be needed to know their variance.

The genetic parameters (e.g. heritability) for most quantitative traits can be estimated using classical procedures, since these traits are approximated using normal distributions. The heritability of any trait reflects the proportion of the total variance that is attributed to differences in breeding values. In addition, the heritability have a predictive aspect, express the reliability of the phenotypic values as a guide to estimate the breeding values, where only the phenotypic values of the individuals can be directly measured. In the case of the linear traits, this parameter can be easily estimated through the offspring-parent regression. In contrast, this is not the case for longevity and other functional traits, given the special properties of their data and the nonlinearity nature of the models used in the survival analysis for studying their records. It is no obvious what is the adequate definition of the heritability, and consequently, exist various forms to present this parameter. For this reason, the comparison between different estimates of heritability of different studies should be carried out with caution, taking into account the scale of the estimation.

One of these forms is the heritability on the logarithmic scale $\mathrm{h^2}_{\mathrm{log}}$ that derived for the first time by Ducrocq (1987) for Weibull sire models as $\mathrm{h^2}_{\mathrm{log}} = \frac{4\sigma^2{}_{\mathrm{S}}}{\left(\sigma^2{}_{\mathrm{S}} + \frac{\pi^2}{6}\right)}$, where $\sigma^2{}_{\mathrm{S}}$ is the sire variance. This expression is also the pseudo-heritability defined by Smith (1983) and derived by Korsgaard et al. (1999) for Cox frailty models. The value of $\frac{\pi^2}{6}$ in the previous equation is the variance of an extreme value distribution, the distribution of the residual term of log (t) in the proportional hazard models. However, Ducrocq (1999) showed that this heritability is not convenient for the calculation of reliability, i.e. it does not properly represent the reliability of the phenotypic values as a guide to estimate the breeding values, leading to strongly biased values when the reliability (R) of a particular sire is computed using the usual reliability formula such as in selection index for sire evaluation in which $\mathrm{R} = \frac{\mathrm{nh^2}}{(\mathrm{n}-1)\mathrm{h^2}+4}$, where n is the total number of progeny of the sire and $h^2 = h^2_{\mathrm{log}}$. Moreover, Ducrocq (1999) found that it appeared much more appropriate to use the number of uncensored progeny in the equation of reliability as well as the heritability of the trait transformed onto the heritability on the original scale $\mathrm{h^2}_{\mathrm{ori}} = \left(\exp\left(\frac{\nu}{\rho}\right)\right)^{-2} \mathrm{h^2}_{\mathrm{log}}$ where ν is the -Euler´s constant equal to -0.5772 and ρ is the shape parameter of the baseline Weibull distribution. By using Taylor series approximations for the ratio of genetic variance to phenotypic variance, Korsgaard et al. (1999) suggested that heritability on the log scale is also appropriate on the original scale.

An alternative derivation using basic expressions of reliabilities in sire models suggested a simple equation for the heritability on the original scale (called hereafter effective heritability, $h^2{}_{eff} = \frac{4\sigma^2{}_S}{(\sigma^2{}_S+1)}$) that is not dependent on the Weibull parameters (Yazdi et al., 2002). The differences between these heritabilities and those from using the previous equations are small when ρ = 2.0 (Ducrocq, 1999) but can be huge when ρ is far from special value such that the correcting term in the equation of the effective heritability is close to $\frac{\pi}{6}$. The reliability for sire breeding value predictions from the Weibull models is calculated using the number of uncensored progeny (n_{uncen}) and the sire variance as $R_{Wei} = \frac{n_{uncen}}{\left(n_{uncen}+\frac{1}{\sigma^2{}_S}\right)}$.

The effective heritability estimates are maximum values, considering that all records are uncensored, this means that increasing censoring rate decreases the heritability estimate. If the proportion of the sire progeny that have not survived until a given time t is $\overline{P}$, an equivalent heritability ($h^2{}_{equ}$) can be defined as the value of h^2 such that the reliability can be computed using the selection index formula (with n instead of n_{uncen}). The equivalent heritability can be defined as $h^2{}_{equ} = \frac{4\sigma^2{}_S}{\left(\sigma^2{}_S+\frac{1}{\overline{P}}\right)}$, and the reliability using the Weibull model as $R_{Wei} = \frac{n\overline{P}}{\left(n\overline{P}+\frac{1}{\sigma^2{}_S}\right)}$. Both effective and equivalent heritability parameters are derived for the Weibull model without stratification, and without time-dependent covariates. Using these definitions of heritability in the case of using other models does not seem very adequate. However, the value of these parameters for computing approximated accuracies using the Cox model with time-dependent covariates have been validated, the approximated accuracies were compared to accuracies computing using the true prediction error variance and they were very similar (Sánchez, 2006). This validates effective heritability as a parameter that reflects the reliability of the phenotypic values as a guide to estimate the breeding values.

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Chapter 2

OBJECTIVES

This thesis has been developed with the general goal of the evaluation of five Spanish rabbit lines in terms of functional longevity. In order to achieve this goal, the following objectives were defined:

1. To analyse the variability in the genetic determination of functional longevity in the five lines, and to check how different systematic factors might affect this genetic determination.

2. To estimate the genetic and environmental correlations between functional longevity and prolificacy traits, such as number of kits born alive and number of kits at weaning, and to estimate the genetic and environmental correlations between functional longevity and the different physiological statuses in the five lines.

3. To compare the five rabbit lines in terms of functional longevity at foundation and fixed times during their selection processes for reproductive or growth traits, assessing the consequences that the selection process might have on the longevity of each one of the lines.

Chapter 3

Genetic variability of functional longevity in five rabbit lines

3.1 ABSTRACT

The objectives of this study were to analyse the differences in the genetic determination of functional longevity in five Spanish lines of rabbits, and to check how different systematic factors might affect this genetic determination. Four of the lines are maternal (A, V, H and LP) founded on different criteria and being selected for litter size at weaning. The other is the paternal line R, founded and selected for daily growth rate. The trait analysed, length of productive life (LPL), was the time in days between the date of the first positive pregnancy test and the date of culling or death of a doe. Data analysis was performed applying the survival analysis methodology using a Bayesian approach. Four models extended from the Cox proportional hazard model were used to analyse data of each line both separately and jointly. The complete model included the fixed effect of year-season combination (YS), positive palpation order (OPP), i.e. reproductive cycle, physiological status of the doe at service (PS) and number born alive at each kindling (NBA) as time-dependent factors, the inbreeding coefficient was fitted as a continuous covariable (F), in addition the animal's additive genetic effect was fitted as a random effect (Model 1). The other three models were the same as the first one but discarding OPP, PS or NBA (Models 2, 3 and 4). Combined analysis using all data set of all lines was performed using the same model as Model 1 substituting the year-season combination by the line-year-season combination. Estimated effective heritabilities of longevity were 0.07±0.03, 0.03±0.02, 0.14±0.09, 0.05±0.04, 0.02±0.01 and 0.04±0.01 for lines A, V, H, LP, R and for the all data set, respectively. Removing the PS from the model (Model 3) led to an increase in the estimated additive genetic variance in all lines (0.17±0.05, 0.05±0.03, 0.29±0.19, 0.29±0.20, 0.07±0.04 and 0.05±0.02 for lines A, V, H, LP, R and all data set, respectively), this could be an indication of the existence of a relevant genetic correlation between longevity and physiological status, while discarding the OPP or NBA from the model showed to be less important. The hazard of death or culling decreases as the order of parity progresses, the highest during the first two parities. The does that were non-pregnant-non-lactating had the higher risk. The does that had zero born alive had the highest risk of dying or being culled, and the risk decreases as the number of born alive increases. Thus, it can be concluded that some systematic factors have an important influence on the genetic

determination of the trait and although large differences in the genetic determination of LPL might exits, the estimation errors does not allow to discard the hypothesis of all the studied populations to have the same heritability.

Key words: Rabbits, longevity, heritability, Cox proportional hazard model, survival analysis.

3.2 INTRODUCTION

The annual replacement rate in meat rabbits is about 112% (Prieto et al., 2014) with near 50% of the dead or culled does replaced during their first 3 parities (Rosell, 2003). The average pregnancy rate in the Spanish commercial farms is about 78.2% and the average number of parities per doe is 5.7 (personal communication with bdcuni "database of technical management in Spanish rabbit sector"). The main problems associated with this high replacement rate are the cost of the does, the greater proportion of less mature females (young does are still growing and are, immunologically, less mature at parturition, showing lower litter size and more health problems than the adults), and sometimes the management and pathological problems related to introduction of animals from other farms (Piles et al., 2006). Another important point regarding the replacement of an animal becoming ill or dead is its low productive period before the replacement. This point could be important and is not considered in the studies concerning longevity and its economic importance.

Intensive meat rabbit production is based on a three-way crossbreeding scheme, which mainly uses crossbred does, coming from the cross of two maternal lines (Baselga et al., 2004). The length of productive life of the crossbred does will depend on both the longevity of the maternal lines involved in the cross and on heterotic effects that might appear between them; so far, little attention has been paid to extensively studying the longevity in maternal lines.

The only work known that considers rabbit does longevity as a criterion of foundation was the one by Sánchez et al. (2008) that describes the creation of the LP line. In addition, a divergent selection experiment for functional longevity was carried out in the INRA 1077 rabbit line, obtained a difference of longevity between the two lines of 32 days (Larzul et al., 2014), but the symmetry of the response was not assessed. More numerous, but still scarce are the experiments aiming at estimating the heritability of the trait (Piles et al., 2006; Sánchez et al., 2004). These experiments have considered a small number of rabbit lines and have showed the dependency of the estimates on the model of analysis (Garreau et al., 2001). Thus, the objective of this study was to estimate the heritability of the longevity in a set of lines that differ in their histories of foundation and selection, and testing the consequences of different models on the obtained estimates.

3.3 MATERIALS AND METHODS

3.3.1 Animals

Data used in the present study were collected from five Spanish lines of rabbits. Four of them are maternal lines (A, V, H and LP), and the other line is a paternal line (R). Animals were reared at a selection nucleus located in the farm of the Department of Animal Science, Polytechnic University of Valencia (UPV). The records were collected from the foundation of the lines until March 2013.

The process of foundation of line A began in 1976 sampling New Zealand White (NZW) rabbits, reared by farmers near Valencia (Spain). After three generations without selection, the line is being selected since 1980 by a family index based on litter size at weaning (Estany et al., 1989). Line V was founded in 1980 as a synthetic line, crossing crossbred animals that were progeny of four specialized maternal lines, after three generations without selection, the line is being selected (Estany et al., 1989) to increase litter size at weaning since 1982. Line H was founded applying hyperprolific selection and embryo cryopreservation techniques (García-Ximénez et al., 1996; Cifre et al., 1998). Hyperprolific does were assembled from a large commercial population, spread over different Spanish farms. This line was kept since its foundation in 1996 at the nucleus of selection until May, 2004 (10th generation of selection) when it was moved to another farm 180 km north of Valencia (Sant Carles de la Ràpita, Tarragona). Line LP was founded selecting females from commercial farms that showed extremely long productive lives and prolificacy near or above the average of the Spanish commercial rabbit population (Sánchez et al., 2008). This line is being selected since 2003 to increase litter size at weaning. In V, H and LP, animals are evaluated for litter size using BLUP under a repeatability animal model. Line R comes from the fusion of two paternal lines, one founded in 1976 with California rabbits reared by Valencian farmers and other founded in 1981 with rabbits belonging to specialised paternal lines (Estany et al., 1992). The method of selection has always been individual selection on post-weaning daily gain.

The last generations of selection considered in the present study were 44th, 39th, 10th, 8th and 32nd for lines A, V, H, LP and R, respectively. The selection of the maternal lines is conducted in non-overlapping generations, does for the next generations are selected from 25 – 30 % of the best evaluated matings, with a limit of 4 does per mating. Each sire contributes a son to the next generation, and is selected from the best mating of the sire.

The farm where the rabbits are housed has isolated roofs and ventilation controlled, depending on the indoor temperature. The cages for does (90 cm long, 50 cm wide and 40 cm high) and progeny (80 cm long, 50 cm wide and 30 cm high) are standard flat deck. Management of animals in the different lines is the same, using natural mating, bucks and does began reproduction from 17 to 18 weeks of age. On the day 12 post-mating each doe is tested for pregnancy by abdominal palpation, and non-pregnant does are mated back. Does are mated 11 days after kindling, generally one female is always mated to the same buck, litters are examined each morning during the suckling period to remove the dead kits. Kits are reared by their own dams, and weaned at 28 days post kindling. Then animals are individually identified by a number tattooed on the left ear and transferred to the fattening cages (8-9 rabbits per cage) until marketing at 63 days. Both breeding animals and progeny are fed *ad libitum* on pelleted commercial rations. The animals were kept under controlled 16-h light: 8-h dark photoperiods.

For a suitable genetic evaluation of animals in the nucleus, some common culling criteria in commercial farms are not considered; i.e. does with low levels of production or no strong reproductive delay are not culled.

3.3.2 Trait and Statistical Models

The longevity of a doe (length of productive life, LPL) was measured as the difference between the date of the first positive palpation test and the date of death or culling for involuntary causes (Sánchez et al., 2008). Once again, does were never culled based on production results, therefore, LPL reflected a direct measurement of functional longevity. Date and reason for culling or death are systematically recorded, as well as all the information regarding mating and parturition dates, pregnancy status after the abdominal palpation and prolificacy. Does removed to free space to females of the next generation or eliminated because of accidents or other technical reasons not related to health status were treated as censored (Piles et al., 2006). Thus, the record of each animal included the called censoring code, representing (0 = censored; 1 = uncensored) and all the information regarding physiological status of the female during its entire life (reproductive and lactation status), as well as all the prolificacy records and the line to which the animal belonged. Functional longevity was analysed using Cox models. A Weibull model was discarded because of its misfit due to the high proportion of does dying in the first parturition (Sánchez et al., 2004; Piles et al., 2006). The number of does with records was 15,670 and the pedigree involved 19,405 animals. Out the total number of females with records 5,775 were censored (Table 3.1), part of these does were removed before the end of their productive life because of space limitations in the nucleus and the followed breeding program.

A first analysis was done with a model that was called Model 1 or complete model which equation was:

$$\begin{aligned} h_i\left(\mathrm{t}|\mathbf{x}'_{\boldsymbol{i}}(\mathrm{t})\right) \;=\; h_0\ (t)\exp\ \{ & \mathbf{x}'_{\boldsymbol{i}}(\mathrm{t})_{\mathbf{YS}}\,\boldsymbol{\beta}_{\mathbf{YS}} + \mathbf{x}'_{\boldsymbol{i}}(\mathrm{t})_{\mathbf{OPP}}\,\boldsymbol{\beta}_{\mathbf{OPP}} + \mathbf{x}'_{\boldsymbol{i}}(\mathrm{t})_{\mathbf{PS}}\,\boldsymbol{\beta}_{\mathbf{PS}} \\ & + \mathbf{x}'_{\boldsymbol{i}}(\mathrm{t})_{\mathbf{NBA}}\,\boldsymbol{\beta}_{\mathbf{NBA}} + \mathrm{F}_i\,\beta_{\mathrm{F}} + \mathbf{z}'_i\,\mathbf{u}\} \end{aligned}$$

where $\mathrm{h_i(t|}\mathbf{x}'_{\mathrm{i}}\mathrm{(t))}$ is the hazard of animal i at time t, for time-dependent factors, affected by covariates indicated by $\mathbf{x}_{\mathbf{i}}'(\mathrm{t})=\{\mathbf{x}_{\mathbf{i}}'(\mathrm{t})_{\mathbf{YS}}, \mathbf{x}_{\mathbf{i}}'(\mathrm{t})_{\mathbf{OPP}}, \mathbf{x}_{\mathbf{i}}'(\mathrm{t})_{\mathbf{PS}}, \mathbf{x}_{\mathbf{i}}'(\mathrm{t})_{\mathbf{NBA}}, \mathrm{F}_i, \mathbf{z}_{\mathbf{i}}'\}$; $\mathrm{h_0(t)}$ is the baseline hazard function at time t, defined by a step-wise function given by $h_0(t) = h_{0m}$ for $\mathrm{t} \in [\tau_{m-1}, \tau_m]$; $m = 1, \ldots, M + 1$, where $\tau_1, \ldots, \tau_M$ are the M different ordered survival times, $\tau_0 < \tau_1 < \cdots < \tau_M < \tau_{M+1}$; $\tau_0 = 0$ and $\tau_{M+1} = \infty$. $\boldsymbol{\beta}_{\mathbf{YS}}$, is the vector of regression coefficients comprising the effects of year-season (**YS**) combinations. It was defined by 6 months' time intervals and the number of levels was 63, 63, 17, 20 and 49 for the subsets of A, V, H, LP and R lines, respectively. This factor accounts for the effect acting over all the contemporary animals in the farm. When a joint analysis of all lines was conducted, YS was substituted by line-year-season combination (**LYS**) with 212 levels. The line effect comprised 5 levels (A, V, H, LP and R). $\boldsymbol{\beta}_{\mathbf{OPP}}$ **,** is the vector including the effect of the three levels of the positive palpation order (**OPP**) (1, 2 and 3 or more positive palpation orders), the changes of level in this factor occurred after every pregnancy test. $\boldsymbol{\beta}_{\mathbf{PS}}$**,** is the vector including the effects of the physiological status of the female, it comprised 6 levels, this factor reflects the combination between the reproductive status of the doe (pregnant, non-pregnant, and unknown), and its lactation status (lactating and non-lactating). With regard to lactation status, changes of level occurred at parturition and at weaning, while for reproductive status the changes of the levels might occur at mating, after pregnancy test and at parturition; the unknown level included does in the period between mating and the pregnancy test. $\boldsymbol{\beta}_{\mathbf{NBA}}$, is the vector including the effects of 5 classes of number born alive in each kindling (**NBA**); the first level corresponded to does that had 0 NBA, the second level to does that had 1 to 4 born alive, the third to 5 to 8 born alive, and so on until the fifth level which corresponded to does that had at least 12 born alive. The changes of levels in this time-dependent factor occurred at parturition. Because only females with at least one litter were considered in the analysis, there were no nulliparous does. β_{F} is the time-independent linear regression coefficient on the inbreeding coefficient of animal i (F_{i}). Finally, $\mathbf{u}$ is the additive genetic effect of the animal i, this factor was assumed to follow a priori a multivariate normal distribution with mean 0 and (co)variance **A**σ^2_a, where **A** is the numerator relationship matrix and σ^2_a is the additive genetic variance. Prior distributions for the parameters were defined in the same way as in Sánchez et al. (2006b); λ_i were assumed to be i.i.d., $\lambda_i = \frac{1}{\lambda_i}$, the elements of all $\boldsymbol{\beta}$ were assumed to be i.i.d. following a bounded uniform distribution and the additive genetic variance (σ^2_a) was also assumed to follow a bounded uniform distribution. The estimation of model parameters was performed by a Bayesian approach, based on statistics of samples from the marginal posterior distributions obtained using a Gibbs sampling algorithm. The Gibbs sampling was implemented in a Fortran 90 program, in which the subroutines by Gilks and Wild (1992) for adaptive rejection sampling (ARS) were used (Sánchez et al., 2006b) and the program is available upon request from the authors. The Gibbs sampler algorithm comprised 200,000 iterations, discarding the first 20,000. Afterwards, one sample in each 20 was saved and features of interest of the marginal posterior distributions were obtained with the coda package of the R program. Convergence of the chains of the parameters and contrasts of interest was assessed by using the Z-criterion of Geweke (Geweke, 1992). More details about this procedure, can be found in Blasco (2001) and Sorensen and Gianola (2002).

Given the nonlinear nature of the models used in the survival analysis, there is no heritability definition equivalent to that from linear models. One interesting definition of heritability, related to the computation of the accuracy of breeding values predictions is the effective heritability (Yazdi et al., 2002), $h^2{}_{\mathrm{eff}} = \frac{\sigma^2{}_{\mathrm{a}}}{\sigma^2{}_{\mathrm{a}} + 1}$. This formula was developed by Yazdi et al. (2002) for a Weibull sire model. Its extension to a Cox model was validated by J.P. Sánchez for the Cox model through simulation (Ducrocq, 2006).

To check the effects of the systematic factors on the genetic determination of longevity (additive variance estimate), three additional analyses were performed with the same Model 1 but discarding OPP (Model 2), or PS (Model 3), or NBA (Model 4).

3.4 RESULTS AND DISCUSSION

3.4.1 Variability of genetic parameters across lines

Descriptive statistics regarding longevity data of the lines are presented in Table 3.1. As shown in this table the lines H and LP had the highest censoring rates. LP line had a longer LPL compared to the other lines, as expected, as a consequence of its foundation process (Sánchez et al., 2008) and followed by the line V. Lines A and R had a similar LPL for both censored and uncensored records. Percentage of the censored records in line R (19.3%) was markedly lower than those of the other lines. This may be explained by a higher disease incidence in this line compared to the others. This result is in accordance with Sánchez et al. (2012) who found that R line animals had mastitis prevalence and ulcerative pododermatitis of 10.0% and 23% while line V had 4.0% and 9%, respectively. They added that the overall disease index for the lines A, V and R was 32%, 20% and 42%, respectively with significant differences between them.

Table 3.1 Summary statistics for longevity data.

Line	N1[1]	Censored (%)	LPL (d)[3] Censored	LPL (d)[3] Uncensored	N2[2]
A	4,986	35.9	238.0	151.6	6,146
V	5,275	35.7	284.6	175.7	6,423
H	1,156	55.2	235.3	138.4	1,376
LP	1,224	55.7	355.1	208.1	1,425
R	3,029	19.3	240.9	153.9	4,035
All lines	15,670	35.6	268.1	162.6	19,405

[1]N1= Numbers of does in data file; [2]N2= Number of animals in pedigree file; [3]LPL (d) = Length of productive life in days.

The Geweke test did not detect lack of convergence in any case. Estimates of the additive variance and the corresponding effective heritabilities are shown in Tables 3.2 and 3.3. The estimated heritabilities were within the range of the previous estimates and were low. Line H had the highest heritability estimate (0.14) but with a very wide $HPD_{95\%}$ (0.003, 0.292). This low precision is consequence of the low number of records in this line. The paternal line in this study, line R, had the lowest estimate (0.02). The precision was greater in the case of lines A and V due to the larger number of records; in these cases around 40 generations of data were covered. In spite of the large variation of the heritability estimates, the corresponding $HPD95_{\%}$ always overlapped and consequently the hypothesis of all lines having the same heritability cannot be discarded. Taking into account the low estimates of heritability for longevity in the five rabbit populations, it is not recommended to include this trait as selection criteria in rabbit breeding programs.

Table 3.2 Estimates of additive variance for longevity.

Line	PM[1]	PSD[2]	$HPD_{95\%}$[3]	MCE[4]
A	0.08	0.03	0.026 , 0.150	0.004
V	0.03	0.02	0.003 , 0.071	0.003
H	0.18	0.13	0.002 , 0.412	0.011
LP	0.05	0.05	0.000 , 0.144	0.004
R	0.02	0.01	0.000 , 0.045	0.002
All lines	0.05	0.02	0.013 , 0.071	0.002

[1]PM= posterior mean; [2]PSD= posterior standard deviation; [3]$HPD_{95\%}$= highest posterior density region at 95 % of probability; [4]MCE= Monte Carlo error.

In rabbits, Youssef et al. (2000) using REML, estimated heritabilities of 0.08 and 0.13 for number of litters and length of productive life, respectively. In that work they used a linear mixed model ignoring the censored data considering them as complete data, which implies underestimate the LPL of the does. In addition they used a sire model to infer the genetic variance, for these reasons our estimates are not comparable with theirs.

Sánchez et al. (2006b) including a residual term in the model, reported an additive variance of 0.25 (posterior mean) and a residual variance of 0.69 which corresponds to an effective heritability of 0.19 in a replicate of line V.

Other estimates of the heritability for longevity were reported by Piles et al. (2006) who stated that despite the differences in breeding schemes, voluntary culling rules, definition of reproductive longevity, and modelling of the baseline hazard function, effective heritabilities of longevity obtained in the Prat and A1077 lines were quite similar. Using the model with the physiological status, these estimates were 0.158 and 0.172 in Prat and A1077 lines, respectively, while using the model without this factor the corresponding estimates were 0.237 and 0.187. Recently, Larzul et al. (2014) using a sire-maternal grandsire model, reported an effective heritability of 0.185 for longevity in INRA 1077 line measured as the total number of artificial inseminations.

Table 3.3 Estimates of effective heritability for longevity.

Line	PM[1]	PSD[2]	$HPD_{95\%}$[3]	MCE[4]
A	0.07	0.03	0.024 , 0.130	0.003
V	0.03	0.02	0.003 , 0.066	0.002
H	0.14	0.09	0.003 , 0.292	0.008
LP	0.05	0.04	0.000 , 0.126	0.004
R	0.02	0.01	0.000 , 0.043	0.002
All lines	0.04	0.01	0.013 , 0.066	0.002

[1]PM= posterior mean; [2]PSD= posterior standard deviation; [3]$HPD_{95\%}$= highest posterior density region at 95 % of probability; [4]MCE= Monte Carlo error.

In pigs, Yazdi et al. (2000) found estimates of heritability for LPL varying from 0.109 to 0.268. Serenius and Stalder (2004) reported heritabilities of 0.16 and 0.19 for LPL in Landrace and Large White pig populations. Other studies indicated that the estimates of heritability ranged from 0.06 to 0.4 (Engblom et al., 2009 and Mészáros et al., 2010).

Results from models 1 and 3 are compared in Table 3.4, correcting for physiological status of the female removed about 51, 39, 38, 83 and 75% of the additive variance in lines A, V, H, LP and R, respectively. Hence, part of the genetic differences for functional longevity can be said to be related to the way in which the risk of the females changed with the physiological status and to the genetic determination of the physiological status. These findings are in agreement with those reported by Piles et al. (2006) who found that in Prat line the correction for physiological status removed about 40% of the additive variance.

The important changes in genetic variance in some lines when removing the physiological status from the model could be an indication of the existence of a higher genetic correlation between longevity and physiological status in them. A genetic correlation between longevity and physiological status could be expected if is taken into account that both are affected by the fertility and health of the does. But more studies are needed to check this speculation. In the same context, in dairy cows Zavadilová and Zink (2013) reported that the genetic correlations of longevity with fertility were moderate and favourable.

Table 3.4 Posterior means (posterior standard deviations) of the additive variance for longevity using different models.

Line	Model 1	Model 2	Model 3	Model 4
A	0.08(0.03)	0.07(0.03)	0.17(0.05)	0.07(0.03)
V	0.03(0.02)	0.03(0.02)	0.05(0.03)	0.02(0.02)
H	0.18(0.13)	0.13(0.10)	0.29(0.19)	0.18(0.12)
LP	0.05(0.05)	0.04(0.04)	0.29(0.20)	0.03(0.03)
R	0.02(0.01)	0.01(0.01)	0.07(0.04)	0.02(0.01)
All lines	0.05(0.02)	0.04(0.01)	0.05(0.02)	0.05(0.02)

Model 1= YS + OPP + PS + NBA + F + animal; Model 2= YS + PS + NBA + F + animal = (Model 1 – OPP); Model 3= YS + OPP + NBA + F + animal = (Model 1 – PS); Model 4= YS + OPP + PS + F + animal = (Model 1 – NBA).

In the LP line, the change in additive variance was about 83% which could be related to the highest values in this line of the contrasts between different levels of the physiological status showed in Table 3.7. Later on it is indicated that this highest values could be a consequence of the foundation criterion of this line that increased the average longevity and could produce a range effect on other factors affecting the trait.

The effect of accounting for number born alive in the model is shown in Table 3.4, by comparing results of Models 1 and 4 in Table 3.4. The correction for number born alive slightly changed the additive variance of longevity in all lines, this could be an indication of the low genetic correlation between prolificacy and functional longevity previously estimated as very low and not significantly different from zero (Sánchez et al., 2006a). The same trend was observed when comparing the results from Models 1 and 2 (Table 3.4), there were no relevant changes in the additive variance when correcting for the positive palpation order.

3.4.2 Genetic trends

Figure 3 shows the genetic trends for the different lines that were computed as the posterior means of the expected breeding values for the log hazard of the animals born in a given generation. Animals with the more negative breeding values are those with the higher longevity and vice versa. The highest slopes of the genetic trend were observed for lines H and A. The differences in genetic trend between lines can be partly explained by the differences of the heritability (Table 3.3), as well as the differences in intensity of natural or unintended selection for longevity in the different lines. Correlated response is not expected to be responsible of the observed trend, since the genetic correlations with the selection criteria, as will be see latter in Chapter 4, are low. Here, the importance of natural or unintended selection in a line is clearly related to its longevity, animals with lower longevity have higher probability of dying before leaving progeny to be selected as reproducing animals for the next generation. Consequently, the high genetic trend observed in lines A and H is due to their relatively higher heritabilities (Table 3.3) and to their low longevities (Table 3.1). Despite the low longevity of line R (Table 3.1), its genetic trend was low which may be explained by its extremely low heritability (0.02).

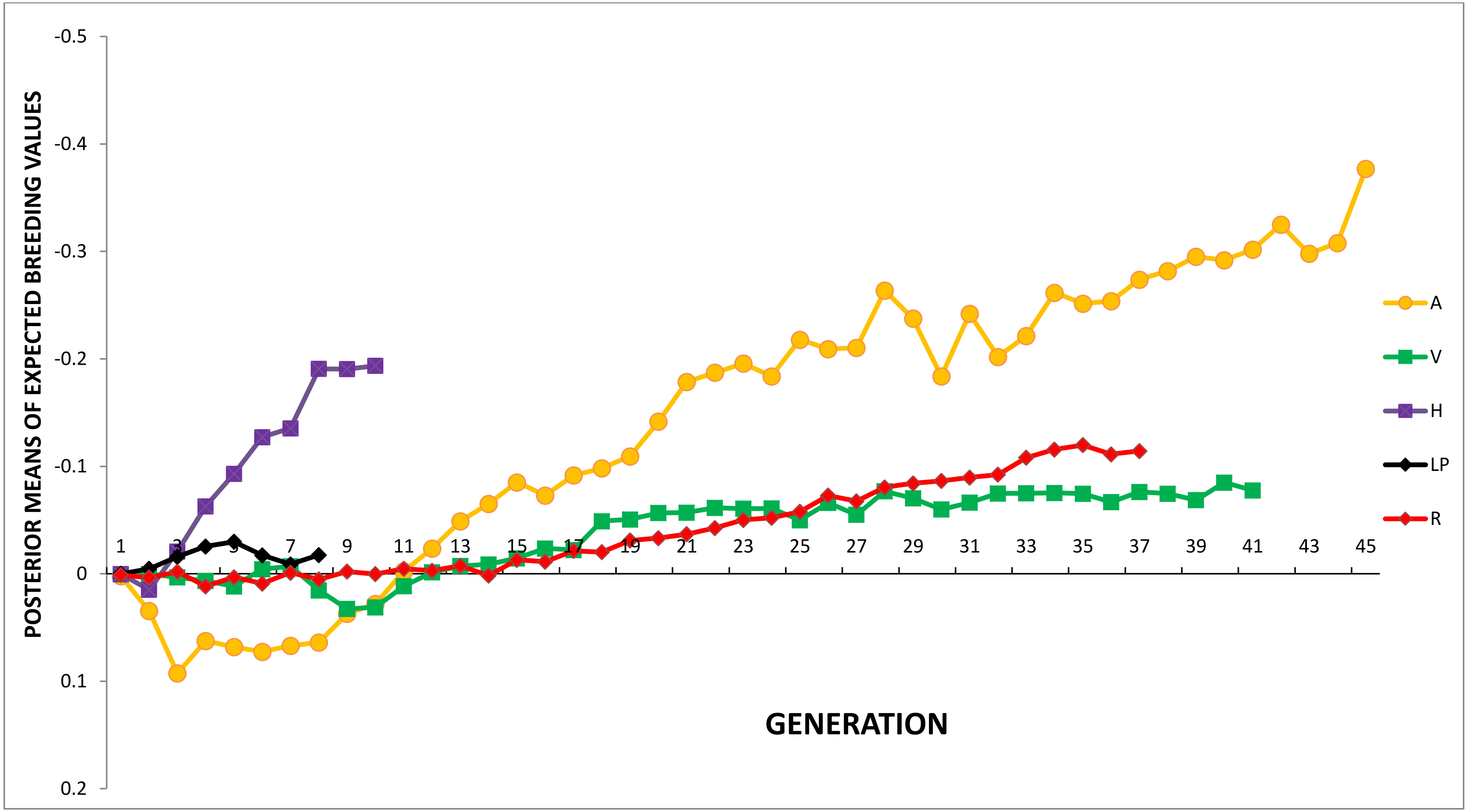

Figure 3 Genetic trend for hazard by line using the analyses of lines separately.

3.4.3 Inbreeding depression

The posterior means and standard deviations of the inbreeding depression affecting the log hazard are presented in Table 3.5. It has not been possible to confirm that the effect of the inbreeding depression is significantly different of zero due to the high standard errors of the estimates. This can be due to the colinearity between the inbreeding and year-season effects; it means that a group of does within the same year-season tends to have the same inbreeding level. This colinearity makes the separation of the two effects in the model of analysis difficult.

In pigs, Casellas et al. (2008) studied the founder-specific inbreeding depression effects (FSID) on the longevity of Landrace sows and reported that all models of analysis were consistent with an overall negative genetic effect of inbreeding on sow longevity. However, the analyses highlighted considerable variability in FSID effects, with unfavourable, neutral and even favourable influences on sow longevity. They added that the founders with the worst inbreeding depression effect reduced sow longevity by 32 days for 1% or 167 days for 10% of partial inbreeding.

Table 3.5 Estimates of inbreeding depression affecting longevity.

Line	**PM**[1]	**PSD**[2]	**$\mathbf{HPD_{95\%}}$**[3]	**MCE**[4]
A	-0.22	1.72	-3.64 , 3.12	0.09
V	0.41	1.67	-2.77 , 3.69	0.06
H	6.01	3.10	-0.14 , 12.08	0.04
LP	6.44	7.68	-9.10 , 20.98	0.13
R	-0.48	0.97	-2.32 , 1.47	0.03

[1]PM= posterior mean; [2]PSD= posterior standard deviation; [3]$HPD_{95\%}$= highest posterior density region at 95 % of probability; [4]MCE= Monte Carlo error.

3.4.4 Systematic effects on functional longevity

3.4.4.1 Positive Palpation Order (OPP)

Posterior means and standard deviations of the contrasts of log-hazard between the different levels of the positive palpation order (OPP) are presented in Table 3.6. The differences between the positive palpation orders were relevant. The probabilities of these differences being greater than zero were between 99 and 100% in 12 out of 15 contrasts. The results showed that the hazard decreased as the parity order advanced. The highest differences of hazard were observed between OPP1 and OPP3, followed by the contrasts between OPP2 and OPP3. The maximum difference of hazard between the first and third level of OPP was in the LP line (1.30±0.34). The selection conducted when founding this line, extremely long-lived animals, would promote survival ability at later ages rather than at early ages (Sánchez et al., 2008).

The hazard of death or culling was greater for the first two parities, this could be explained as in the first parity the does are still growing and the kindling would be an important risk factor (Sánchez et al., 2004). In line V, does in OPP1 always had the highest risk followed by does in OPP2 and OPP3 (Sánchez et al., 2006b). The same trend was observed by Lenoir et al. (2013) in the Hycole line D, and reported that the hazard was greater for does in the first parity (1.47) than for those in the second parity (1.22). The lowest risk was found for the third parity (1.00). The results of the present study are in agreement with those by Rosell, (2003) who indicated that 50% of the rabbit does die or are culled during the first three kindlings. In pigs, young sows are being removed at a higher rate for reproductive problems when compared with older sows (Lucia et al., 1996; Boyle et al., 1998). On the contrary, Tarrés et al. (2006) reported that the risk of sow’s removal increased with higher parity numbers as well as with decreasing litter size (Friendship et al., 1986; Yazdi et al., 2000).

Table 3.6 Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of positive palpation orders affecting longevity.

Line Contrast	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
OPP1 – OPP2	0.26(0.08)	99	0.19(0.09)	99	0.30(0.19)	94	0.31(0.23)	91	0.24(0.08)	99
OPP1 – OPP3	0.56(0.13)	100	0.31(0.13)	99	0.84(0.29)	99	1.30(0.34)	100	0.61(0.12)	100
OPP2 – OPP3	0.31(0.08)	100	0.11(0.08)	92	0.54(0.18)	99	0.99(0.22)	100	0.38(0.08)	100

OPP1= 1st order of positive palpation; OPP2= 2nd order of positive palpation; OPP3= 3rd order of positive palpation or more; P(%) = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

3.4.4.2 Physiological Status (PS)

The posterior means and standard deviations of the contrasts of log-hazard between the different levels of the physiological status of the doe at mating (PS) are presented in Table 3.7. The PS reflects the combination between the reproductive and the lactation statuses of the doe. The results showed that the non-pregnant-non-lactating level (NP/NL) had higher risk than the other levels in each one of the five lines, showing that the low fertility of the does in this level is an indication of health's and/or stress problems. In addition, it seems that the lactation status of the doe at mating had relatively higher importance than reproductive status. The same pattern was observed by Sánchez et al. (2004) in a replicate of the V line who found that non-pregnant does at 28 days after kindling had a greater risk of culling than pregnant does within 28 days after kindling. Similarly, Piles et al. (2006) in the A1077 line reported that the relative risk increased for non-suckling does which corresponded to unsuccessful artificial insemination. Sánchez et al. (2006b) found that for a given level of OPP (1^{st}, 2^{nd} or ≥3), the physiological state "Empty" was always the level with the highest relative risk followed by "Pregnant", "Lactating" and "Pregnant&Lactating". The same findings were reported by Lenoir et al. (2013) who stated that the risk of survival was lower for non-lactating females at the time of artificial insemination than for the lactating females of the commercial line D. In pigs, Anil et al. (2008) stated that farrowing has been reported to be an important risk factor for sow mortality.

Table 3.7 Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of physiological status affecting longevity.

Line Contrast	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
WITHIN LACTATIONAL STATUS										
U/NL – P/NL	0.76(0.07)	100	0.47(0.07)	100	0.29(0.18)	94	0.47(0.20)	99	0.89(0.08)	100
U/NL – NP/NL	-0.86(0.06)	100	-1.20(0.06)	100	-0.83(0.15)	100	-2.02(0.15)	100	-0.54(0.06)	100
P/NL – NP/NL	-1.63(0.06)	100	-1.67(0.06)	100	-1.12(0.15)	100	-2.50(0.15)	100	-1.43(0.07)	100
U/L – P/L	-0.55(0.11)	100	-0.32(0.13)	99	0.36(0.40)	81	1.02(0.85)	90	0.11(0.22)	70
U/L – NP/L	-0.68(0.08)	100	-0.58(0.08)	100	-0.45(0.19)	99	-0.78(0.24)	100	-0.18(0.10)	96
P/L – NP/L	-0.13(0.11)	89	-0.25(0.12)	99	-0.80(0.39)	99	-1.80(0.83)	100	-0.29(0.21)	70
WITHIN REPRODUCTIVE STATUS										
U/NL – U/L	1.45(0.08)	100	1.43(0.09)	100	1.23(0.21)	100	1.28(0.26)	100	1.21(0.10)	100
P/NL – P/L	0.14(0.11)	91	0.63(0.12)	100	1.30(0.39)	100	1.83(0.83)	99	0.43(0.21)	98
NP/NL – NP/L	1.64(0.06)	100	2.05(0.06)	100	1.62(0.16)	100	2.53(0.15)	100	1.57(0.07)	100
P/L – NP/NL	-1.77(0.11)	100	-2.31(0.12)	100	-2.43(0.41)	100	-4.33(0.83)	100	-1.86(0.21)	100
P/L – U/NL	-0.91(0.12)	100	-1.11(0.13)	100	-1.59(0.42)	100	-2.30(0.84)	99	-1.32(0.22)	100
NP/L – P/NL	-0.02(0.06)	41	-0.38(0.06)	100	-0.50(0.15)	100	-0.03(0.17)	56	-0.14(0.08)	95
NP/L – U/NL	-0.78(0.07)	100	-0.85(0.07)	100	-0.79(0.18)	100	-0.50(0.20)	99	-1.03(0.08)	100
U/L – NP/NL	-2.32(0.08)	100	-2.63(0.08)	100	-2.07(0.19)	100	-3.30(0.23)	100	-1.75(0.10)	100
U/L – P/NL	-0.69(0.08)	100	-0.96(0.08)	100	-0.95(0.19)	100	-0.80(0.25)	100	-0.32(0.10)	100

U= Before palpation test; P= After positive palpation test; NP= After negative palpation test; L= Lactating; NL= Non-lactating; P(%) = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

3.4.4.3 Number Born Alive (NBA)

The posterior means and standard deviations of the contrasts of log-hazard between the different levels of the number of kits born alive are presented in Table 3.8. In line H the probabilities of the contrasts being higher (positive contrasts), or lower than zero (negative contrasts) were between 52 and 91%. These results indicate that either these contrasts have a low magnitude or that the uncertain about them is high. Given the reduced number of records of the H line, for some cases although the contrast reached relevant magnitudes the probability of them to be greater than zero did not reach extreme values.

In the other four lines, the level of zero born alive (A) had a higher risk compared with the other levels. In addition, in line V the level of 1 to 4 born alive (B) had higher risk than the levels of 5 to 8 (C) and 9 to 12 (D) born alive. The association between litter size and doe longevity could be explained by the practice in commercial farms of culling the does with small litters, but in the current study no voluntary culling for productive reasons was practiced in the farm. Thus, the greater risk of culling related to low litter sizes could be associated with underlying pathological and/or stress disorders.

In the present study, longevity of rabbit does of the five lines were not unfavourably affected by large number born alive, and the risk of culling or death decreased with increasing the number born alive, the same pattern was previously observed by Garreau et al. (2001), Sánchez et al. (2006b) and Lenoir et al. (2013). Similarly, Tudela et al. (2003) reported that increasing litter size by selection did not increase culling rate. In the same context, Sánchez et al. (2006a) showed that in line V, longevity and litter size were not antagonistic traits and the genetic correlations between longevity and number of born alive and number at weaning were 0.16±0.09 and -0.17±0.11, respectively. Also, in an experiment comparing a rabbit line selected for litter size over seven generations with a control line, no differences were found in longevity (Rinaldo and Bolet, 1988). In pigs, Serenius et al. (2006) reported that there was no clear association between litter size and LPL when culling for poor reproductive performance was not practiced using a different field data set and comparing 6 different genetic lines.

Analysing the relative importance of the contrasts between the different levels of the systematic effects considered (Tables 3.6, 3.7 and 3.8) is noticeable that the LP line had the maximum magnitude of the contrasts. This result could be considered as a range effect due to the criterion of foundation of this line that increased its longevity and the range of the systematic effects of the factors affecting the trait.

Table 3.8 Posterior means (posterior standard deviations) of the contrasts (log-hazard) between the levels of number born alive affecting longevity.

Line Contrast	A	P(%)	V	P(%)	H	P(%)	LP	P(%)	R	P(%)
B – A	-0.28(0.10)	100	-0.16(0.09)	96	-0.04(0.27)	56	-0.83(0.25)	100	-0.55(0.08)	100
C – A	-0.30(0.09)	100	-0.36(0.08)	100	-0.01(0.22)	53	-1.15(0.16)	100	-0.57(0.07)	100
D – A	-0.30(0.09)	100	-0.42(0.07)	100	-0.15(0.20)	78	-1.21(0.14)	100	-0.48(0.07)	100
E – A	-0.35(0.11)	100	-0.32(0.08)	100	0.01(0.21)	52	-1.40(0.17)	100	-0.43(0.15)	100
C – B	-0.02(0.07)	62	-0.20(0.08)	99	0.03(0.21)	54	-0.32(0.24)	91	-0.02(0.06)	65
D – B	-0.02(0.07)	62	-0.26(0.07)	100	-0.11(0.20)	72	-0.39(0.23)	95	0.07(0.06)	84
E – B	-0.07(0.10)	75	-0.15(0.08)	97	0.05(0.21)	59	-0.57(0.25)	98	0.12(0.15)	79
D – C	-0.01(0.04)	52	-0.06(0.04)	91	-0.14(0.12)	86	-0.07(0.13)	70	0.09(0.05)	95
E – C	-0.05(0.09)	72	0.04(0.06)	77	0.03(0.15)	57	-0.25(0.17)	93	0.14(0.15)	83
D – E	0.05(0.08)	72	-0.10(0.05)	98	-0.16(0.12)	91	0.18(0.14)	91	-0.05(0.15)	65

A= Zero born alive; B= 1 to 4 born alive; C= 5 to 8 born alive; D= 9 to 12 born alive; E= More than 12 born alive; P(%) = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

3.5 CONCLUSIONS

The estimates of effective heritability for functional longevity in the five lines were low, and it is not recommended to include this trait as selection criteria in rabbit breeding programs. However, large differences in the genetic determination of longevity might exits, but the estimation errors does not allow to discard the hypothesis of all the studied populations to have the same heritability. By correcting for physiological status of the female a relevant part of the additive variance for longevity was removed, particularly in line LP, and this result could be related to its foundation criteria. However, discarding the positive palpation order or the number of kits born alive from the model of analysis affected slightly the estimate of the additive variance. The lines that had relatively higher additive variance and lower longevity had stronger response in longevity, most likely as consequence of unintended or natural selection. The hazard decreases as the order of parity progresses, the highest during the first two parities. The non-pregnant-non-lactating level of physiological status had the higher risk of death or culling compared with the other levels, this is an indication of diseases and/or pathological low fertility. The does that had zero born alive had the highest risk of dying or being culled, and the risk decreases as the number of kits born alive increases. This effect was no important for the line H, and this could be related with the criterion of foundation of this line, based on hyperprolificacy.

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Chapter 4

Genetic and environmental relationships of prolificacy and physiological statuses with functional longevity in five rabbit lines

4.1 ABSTRACT

A two-step approach was conducted to estimate the genetic and environmental correlations between functional longevity, defined as length of productive life (LPL), and the prolificacy traits, number of kits born alive (NBA) and number of kits at weaning (NW), and between longevity and the percentage of days that the doe spent in the different physiological statuses with respect to its entire productive life in five Spanish rabbit lines. Four of them are maternal lines (A, V, H and LP) and the other is a paternal line (R). These lines are different in their foundation backgrounds and in their selection history. The first step consists on conducting a single-trait analysis to get the estimates of the genetic and residual variance and to calculate pseudo-records of the traits and their associated weights. The second step estimates genetic and residual covariances, performing two-trait analysis between the pseudo-records of longevity and the pseudo-records of prolificacy and the percentage of days in the different physiological statuses, using the associated weights and variances estimated in the first step. The pedigree file comprised 19,405 animals. The datasets included records of 15,670 does which had 58,329 kindlings and 57,927 weanings recorded from 1980 till 2013. The genetic correlation estimates between LPL and NBA were 0.01(0.01), 0.01(0.01), 0.16(0.20), 0.09(0.02) and -0.12(0.33) for A, V, H, LP and R lines, respectively. Moreover, between LPL and NW they were 0.01(0.02), 0.01(0.01), 0.17(0.23), 0.11(0.02) and -0.44(0.53) for the same lines, respectively. The environmental correlation estimates between LPL and NBA were -0.01(0.01), -0.02(0.01), -0.07(0.05), -0.04(0.04) and 0.01(0.03) for A, V, H, LP and R lines, respectively. Likewise, between LPL and NW they were -0.05(0.02), -0.05(0.01), -0.12(0.05), -0.10(0.04) and -0.05(0.03) for the same lines, respectively. The positive values of the genetic correlations represent unfavourable relationship between longevity and prolificacy, because longevity has been modelled through the hazard. Given the standard errors, and the values of the estimated genetic and environmental correlations, these correlations can be considered as negligible and not significantly different from zero. Consequently, longevity and prolificacy cannot be considered as antagonistic objectives of selection There were evidences of non-negligible genetic correlations between the doe's longevity and the percentage of days she spent in each physiological status for the five lines of rabbits, although, it has not been possible to prove that they were significantly different of zero due to the high standard errors of the estimates. Moreover, the environmental correlations were important and significantly different of zero. These results show that longevity and physiological status are correlated, probably through the influence of fertility and health of the doe in both traits.

Key words: Rabbits, longevity, litter size, fertility, physiological status, genetic correlation.

4.2 INTRODUCTION

Longevity or length of productive life of a rabbit doe is a trait of economic importance as increasing longevity decreases culling rates, and its negative consequences on production, and increases the opportunity to make voluntary culling as well. Despite of its importance, until recently longevity has never been included as selection criteria in rabbit breeding programs. Selection programs in maternal lines were mainly focused on objectives related to prolificacy such as litter size at birth or at weaning (Estany et al., 1989; Rochambeau et al., 1998; Baselga and Garcia 2002), while, in paternal lines, the selection programs were concentrated on goals related to growth traits such as feed conversion ratio through daily weight gain or individual weight at a certain age (Baselga, 2004). However, in a selection program it is important to know the genetic correlations between the criterion of selection and other important economic traits such as growth traits, milk production and longevity, in order to predict the correlated responses and assess the consequences on these traits.

Multivariate analyses between longevity and other economic traits present theoretical difficulties (Ducrocq, 1999) and approximate, non-standard methods, have to be used (Ducrocq, 2001; Ducrocq et al., 2003; Tarres et al., 2006; Damgaard and Korsgaard, 2006; Martínez Ávila and Garcia Cortés, 2007). These difficulties have limited this type of studies, which are particularly scarce in rabbits. Ducrocq et al. (2001) proposed a two-step approach for multiple trait evaluation for functional and production trait. Another procedure is the bivariate quantitative genetic model proposed by Damgaard and Korsgaard (2006) assuming that the unobserved log-frailty scale of the survival trait and the linear trait followed a bivariate normal distribution, including a Gaussian residual for the survival trait correlated with the residual term of the linear trait. In this model the extreme value distributed residual in the log-time scale was assumed to be independent of the linear trait. A recursive model to jointly analyse linear and survival traits was suggested by Martínez Ávila and Garcia Cortés (2007) considering that the productive (linear) trait depends on the phenotype of the survival trait, this means that one source of variation is given by the inclusion of the phenotype of the longevity trait in the description of the production trait, thus, the linear trait maintain its specific distribution and the environmental correlation between the traits is not needed to be explicitly defined, which is the major problem that all these approaches try to avoid, since there is not a bivariate distribution having the extreme value and the normal as marginal distributions. Furthermore González-Recio and Alenda (2007) proposed a sequential threshold model to perform a bivariate analysis for one discrete-time survival trait and a Gaussian trait.

To our knowledge, in rabbits, the only study performed to examine the relationship between longevity and litter size traits was by Sánchez et al. (2006), referred to a replicate of line V and data recorded for ten years, in this case the procedure proposed by Ducrocq et al. (2001) was used. The aims of the present study were to estimate the genetic and environmental correlations between longevity and litter size traits (number of kits born alive (NBA) and number of kits alive at weaning (NW)), in four different Spanish maternal rabbit lines and one Spanish paternal rabbit line, different in their genetic background at foundation, and in their selection programmes, involving data recorded from 1980 until 2013. Also, to estimate the genetic and environmental correlations between doe’s longevity and the percentage of days she spent in each physiological status with respect to its entire productive life.

4.3 MATERIALS AND METHODS

4.3.1 Animals and recorded traits

Data used in the present study were collected from five Spanish lines of rabbits, four of them are maternal (A, V, H, LP) and the fifth one is a paternal line (R). These lines are reared at a selection nucleus located in the farm of the Department of Animal Science, Polytechnic University of Valencia (UPV). The records were collected along the generations of selection of these lines from March 1980 to March 2013. The processes of foundation and selection and management programs of these lines were explained in Chapter 3. The data set included reproductive records of the five lines from their foundation until September 2013, involving 15,670 does which had 58,329 kindlings and 57,927 weanings (Table 4.1).

Table 4. 1 Descriptive statistics of the data files in the different lines.

Line	N1[1]	N2[2]	N3[3]	N4[4]
A	4,986	17,090	17,021	6,319
V	5,275	22,237	21,921	6,423
H	1,156	4,167	4,150	1,376
LP	1,224	6,544	6,544	1,425
R	3,029	8,291	8,291	4,035
Total	15,670	58,329	57,927	19,405

[1]N1= Numbers of does in data file; [2]N2= Number of kindlings; [3]N3= Number of weanings; [4]N4= Number of animals in pedigree.

The pedigree file included a total of 19,405 animals. Individual records of each animal included the date of the first positive pregnancy test and the date of death or culling, the difference between the two dates is the length of productive life of the doe (LPL). The response variables were then the LPL and the censoring codes, a binary code indicating whether animal have a right censored LPL or not, depending on the reason of culling. The records also included date of the different pregnancy tests, the number of young born alive, the number of kits weaned, and the length of the different physiological states, that will be explained in the next section.

To check the hypothesis that was mentioned in the previous chapter, i.e. a high magnitude for the genetic correlation between longevity and the time each animal spent in the different physiological statuses were treated as different traits, calculating the percentage of the number of days that the doe spent in each status with respect to its whole productive life (Table 4.2). Then, the genetic and environmental correlations between LPL and each one of these percentages were estimated.

Table 4. 2 Percentages of days of the whole productive life in each physiological status for each line.

Line / Trait	A	V	H	LP	R
U/NL	16.3	15.4	14.5	14.3	20.3
P/NL	32.3	33	32.4	32.7	31.3
NP/L	23.8	24.6	24.7	25.4	22.8
U/L	17.5	17.3	17.6	17.1	12.2
P/L	3.7	4	3.4	4.1	2.1
NP/NL	6.4	5.7	7.4	6.4	11.3

U= Before palpation test; P= After positive palpation test; NP= After negative palpation test; L= Lactating; NL= Non-lactating.

4.3.2 Statistical Methods

4.3.2.1 General procedure

Ducrocq et al. (2001) proposed a two-step approach for multiple trait evaluation of longevity and production traits. The main approximation relies on the replacement of raw data by pre-adjusted records, free of environmental effects and summarising repeated records of the same animal into a single value. This approximation was tested and obtained unbiased estimates using simulation (Tarres et al., 2006). This means the calculation of a single ‘pseudo-record’ $y^*_{t,i}$ for each animal i and trait t. This ‘pseudo-record’ combines all individual records pre-adjusted for fixed effects and random effects other than the additive effect. The genetic and environmental correlations between longevity and other trait were estimated using a two-trait model of the corresponding “pseudo-records”. The model used for the “pseudo-records” was a random model with additive and residual effects that assumes as fixed the variances of the random effects estimated in single-trait analyses of the original records and are only estimated the covariance between the traits.

4.3.2.2 Pseudo-records for longevity and their associated weight

Longevity data was analysed using the same model as Model 4 (Model 1 excluding the effect of number born alive) described before in Chapter 3. For the calculation of pseudo-records of longevity ($y^*{}_{L,i}$) and their weights ($\omega_{L,i}$), two formulas derived from the equation of Ducrocq et al. (2001) and Sánchez et al. (2006) were used. These equations were:

$$y^*{}_{L,i} = \frac{\delta_i + 1}{\omega_{L,i}} - 1 + \hat{a}_i$$

$$\omega_{L,i} = e^{\hat{a}_i} . \sum_{T_f=1}^{f_i} \left[d_f . \frac{e^{x'_i(T_f) . \hat{\beta}}}{\sum_{j \in R(T_f)} e^{x'_j(T_f) . \hat{\beta} + \hat{a}_j}} \right] + 1 = Cumulative\ hazard_i + 1,$$

where δ_i is the indicator variable which shows if the record of animal *i* is censored ($\delta_i = 0$) or not ($\delta_i = 1$), $\hat{a}_i$ is the estimated breeding value (EBV) of the animal *i*, T_f are the distinct ordered failure times in the whole population, f_i is the time when the animal *i* dies or is censored, d_f is the number of does culled at time T_f , $R(T_f)$ is the group at risk at time T_f and $x'_i(T_f). \widehat{\beta}$ is the sum of all effects affecting animal *i* at time T_f. The weight associated to these pseudo-records of longevity $\omega_{L,i}$ is formed by two terms, the cumulative hazard of animal *i* suggested by Tsiatis (1981) for the Cox model and 1, in this way it is guaranteed that the weights are higher than 1. The analyses were carried out using a the Survival Kit 6.0 program (Ducrocq et al., 2010). The pseudo-records of longevity used for the bivariate analysis with physiological statuses pseudo-records were calculated in the same way as in the case of those used for the joint analysis with prolificacy pseudo-records but using the model excluding the physiological status effects as described before in Chapter 3 (Model 3).

4.3.2.3 Pseudo-records for prolificacy traits and their associated weight

For prolificacy traits (NBA and NW), single-trait repeatability animal models were used to estimate variance components, fixed, additive and permanent environment effects. The models for the two traits were:

$$y_{ijkz} = \mu + YS_k + PS_j + a_i + p_i + e_{ijkz} ,$$

where y_{ijkz} is the z record of NBA or NW trait, μ is the general mean, YS_k is the fixed effect of year-season of kindling or weaning, PS_j is the fixed effect of the physiological state (nulliparous, primiparous suckling, primiparous weaned, multiparous suckling and multiparous weaned), a_i is the additive value of the *i* doe, p_i is the permanent environmental and non-additive effects over all the kindlings of the *i* doe, and e_{ijkz} is the residual. The variance components were REML estimates, obtained using the REMLF90 software (Misztal *et al.*, 2002). The estimated variances were used to estimate the fixed and random effects solving the corresponding mixed model equations using the BLUPF90 software (Misztal *et al.*, 2002). The "pseudo-records" and their associated weights were calculated correcting the raw data for all the model effects other than the additive genetic effects, according to the following equations (Sánchez et al., 2006):

$$y^*_{NBA,i} = \frac{\sum_{z=1}^{n_{NBA,i}}[NBA_{ikjz} - (\hat{p}_{NBA,i} + \widehat{YS}_{NBA,k} + \widehat{PS}_{NBA,j})]}{n_{NBA,i}}, \omega_{NBA,i} = n_{NBA,i}$$

$$y^*_{NW,i} = \frac{\sum_{z=1}^{n_{NW,i}}[NW_{ikjz} - (\hat{p}_{NW,i} + \widehat{YS}_{NW,k} + \widehat{PS}_{NW,j})]}{n_{NW,i}}, \omega_{NW,i} = n_{NW,i}$$

Where $n_{t,i}$ (t = NBA or NW) is the number of kindlings or weanings of the doe *i*. The $\hat{p}$, $\widehat{YS}$, $\widehat{PS}$ are estimates of the permanent environment, year-season and physiological state effects.

4.3.2.4 Pseudo-records for percentage of days in the different physiological statuses and their associated weight

For the six percentages of days in the different physiological statuses, single-trait animal models were used to estimate the additive and residual variances for each trait. The models were:

$$y_{ij} = \mu + YS_j + a_i + e_{ij},$$

where y_{ij} is one of the different percentages of days in the different physiological statuses (U/NL, P/NL, NP/L, U/L, P/L and NP/NL), μ is the general mean, YS_j is the fixed effect of year-season in which the doe began its productive life, and e_{ijk} is the residual. The variance components were REML estimates, obtained using the REMLF90. The estimated variances were used to estimate the fixed and random effects solving the corresponding mixed model equations using the BLUPF90 software. The "pseudo-records" were calculated adjusting the raw data for year-season effects. In these cases the associated weight were 1.0.

4.3.2.5 Validation of the pseudo-records

Before starting with the bivariate analyses between the pseudo-records of longevity and prolificacy, it is important to validate them to be sure that they are correct and represent the original records. For the pseudo-records of longevity, the validation was done by calculating the correlation between the estimated breeding values (EBVs) obtained from the Cox frailty model and the estimated breeding values obtained from the analysis of the "pseudo-records". These "pseudo-records" were analysed assuming a random model with additive and residual effects, additive variance was fixed to that variance estimated with the Cox frailty model and the residual variance was fixed to 1.0; also the data were weighted using their corresponding weights ($\omega_{L,i}$) . For prolificacy traits the validation was done computing the correlation between EBVs from the single-trait repeatability analysis and the EBVs from the analysis of the "pseudo-records" of prolificacy weighted by $\omega_{NBA,i}$ and $\omega_{NW,i}$. For the percentage of days in the different physiological statuses the validation was done computing the correlation between EBVs from the single-trait analysis and the EBVs from the analysis of their "pseudo-records", in this case no differential weighting was done. Similarly to the "pseudo-records" of longevity, the ones for prolificacy and percentage of days in the different physiological statuses were analysed following a random model including additive and residual effects with the variance for them fixed to those estimated in the previous analysis, using the original data and the complete models. The correlations between EBV obtained by both procedures should be close to 1.0.

The model for analysing the pseudo-records with their associated weights can be defined as:

$$y^{*}_{t,i} = \mu_t + a_{t,i} + e_{t,i} \qquad [1]$$

with variances equal to $var[\boldsymbol{a}_t] = \boldsymbol{A}\sigma^2{}_{a,t}; var[\boldsymbol{e}_t] = diag\{1/\omega_{i,t}\}\sigma^2{}_{e,t}$, where $y^{*}_{t,i}$ is the 'pseudo-record' for each animal *i* and trait *t* and $\omega_{i,t}$ is the associated weight.

4.3.2.6 Joint analysis to estimate the genetic and environmental correlations

Two-trait analysis between the "pseudo-records" of longevity and each one of the "pseudo-records" of the prolificacy traits as well as for each one of the percentages of days in the different physiological status traits, considering their weights, were carried out to estimate the corresponding genetic and environmental correlations.

The REML packages used (both programs airemlf90 and remlf90) does not allow for multiple traits weighted analysis, using different weights for each trait. Thus for each one of the traits involved in the bivariate analysis an equivalent random regression model to the model [1] was used:

$$y^{**}_{t,i} = \left(\sqrt{\omega_{i,t}} * {y^*}_{t,i}\right) = \sqrt{\omega_{i,t}} * \mu_t + \sqrt{\omega_{i,t}} * a_{t,i} + e^{**}_{t,i}$$

with variances equal to $var[\boldsymbol{a}_t] = \boldsymbol{A}{\sigma^2}_{a,t}; var[\boldsymbol{e}^{**}_t] = I{\sigma^2}_{e,t}$

Thus, in the bivariate model the distribution of additive genetic and residual effects had the following co-variance matrices:

$$var\begin{bmatrix}\boldsymbol{a}_1\\ \boldsymbol{a}_2\end{bmatrix} = \begin{bmatrix}{\sigma^2}_{a1} & \sigma_{a1,a2}\\ \sigma_{a1,a2} & {\sigma^2}_{a2}\end{bmatrix} \otimes \boldsymbol{A}; \qquad var\begin{bmatrix}\boldsymbol{e}^{**}_1\\ \boldsymbol{e}^{**}_2\end{bmatrix} = \begin{bmatrix}{\sigma^2}_{e1} & \sigma_{e1,e2}\\ \sigma_{e1,e2} & {\sigma^2}_{e2}\end{bmatrix} \otimes \boldsymbol{I}$$

The two-trait analyses were carried out with genetic $({\sigma^2}_{a1}, {\sigma^2}_{a2})$ and residual $({\sigma^2}_{e1}, {\sigma^2}_{e2})$ variances fixed to the estimates obtained in the single-trait analyses of the original data and models, for the case of the longevity, the residual variance has to be fixed to 1.0 (Ducrocq, 2001, Tarres et al., 2006 and Sánchez et al., 2006). Fixing the variances is important in order to obtain unbiased estimates of the correlations (Druet et al., 2003 and Tarres et al., 2006). Initially, remlf90 (Misztal et al., 2002) program – EMREML algorithm - was used, and then using as starting values EMREML estimates airemlf90 (Misztal et al., 2002) program –AIREML algorithm - was run to get final estimates of the correlations as well as their associated errors. When airemlf90 did not converged, remlf90 estimates were retained and the errors were computed evaluating the AIREML hessian matrix at the EMREML estimates. This was done by running airemlf90 only up to the creation of the hessian matrix using as variance components those provided as starting values.

4.4 RESULTS AND DISCUSSION

4.4.1 *Variance components for prolificacy traits*

Variance components, heritabilities and ratios of the permanent environmental variance as a proportion of phenotypic variance and their standard errors for NBA and NW in the different lines are presented in Table 4.3. The heritability estimates ranged from 0.05±0.02 to 0.11±0.01 for NBA and from 0.04±0.02 to 0.12±0.01 for NW. These estimates were in general low values and tended to decrease from birth to weaning. The same trend was observed by Rastogi et al. (2000), who reported that the heritability estimate for NBA and NW were 0.12±0.07 and 0.09±0.07, respectively. The lowest estimates were observed in line H which may be in part due to the foundation criteria followed to create this line which was hyperprolificacy (Cifre at al., 1998). Our estimates are in accordance with those reported by Ragab and Baselga (2011), who stated that the heritability estimate for NBA and NW were 0.10±0.01 and 0.08±0.01, respectively; their estimates were averages of the heritability estimates for A, V, H and LP lines. García and Baselga (2002) in V line reported a heritability estimate of 0.071±0.008 for NBA and 0.047±0.008 for NW. Furthermore, Sánchez et al. (2006), also in V line, found a heritability of 0.15±0.015 for NBA and 0.08±0.011 for NW. The estimates of the ratios of permanent environmental variance to the phenotypic variance ranged from 0.09±0.01 to 0.11±0.02 for NBA and from 0.06±0.01 to 0.13±0.02 for NW. The highest values were observed for the paternal line R. These estimates are similar to those reported by García and Baselga (2002) and Sánchez et al. (2006). Gyovai et al. (2009) in a synthetic maternal line reported a heritability estimate of 0.05±0.03 for NBA and ratio of permanent environmental variance to phenotypic variance of 0.09±0.03 for the same trait. The same parameter was estimated by Rastogi et al. (2000), who found that the permanent environmental variance to the phenotypic variance for NBA and NW were 0.21±0.07 and 0.16±0.07, respectively. Regarding the additive variance of longevity, the Survival kit gave the same estimates as in Chapter 3 using the model without correcting for prolificacy (Model 4).

Table 4. 3 Estimates of variance components and genetic parameters (standard error) of prolificacy traits and longevity in the different lines.

Trait	σ^2_a	σ^2_p	σ^2_e	h^2	p^2
			Line A		
NBA	0.90(0.12)	0.75(0.10)	7.21(0.09)	0.10(0.01)	0.09(0.01)
NW	0.65(0.10)	0.56(0.09)	6.99(0.09)	0.08(0.01)	0.07(0.01)
L	0.07(0.03)	-	1.00	0.08(0.03)	-
			Line V		
NBA	1.21(0.14)	0.92(0.11)	8.56(0.09)	0.11(0.01)	0.09(0.01)
NW	1.09(0.12)	0.55(0.09)	7.53(0.08)	0.12(0.01)	0.06(0.01)
L	0.02(0.02)	-	1.00	0.02(0.01)	-
			Line H		
NBA	0.67(0.27)	1.11(0.28)	10.93(0.28)	0.05(0.02)	0.09(0.02)
NW	0.34(0.17)	0.81(0.20)	8.66(0.22)	0.04(0.02)	0.08(0.02)
L	0.18(0.12)	-	1.00	0.16(0.08)	-
			Line LP		
NBA	0.99(0.27)	1.08(0.23)	8.43(0.16)	0.09(0.03)	0.10(0.02)
NW	0.67(0.20)	0.70(0.18)	7.50(0.15)	0.08(0.02)	0.08(0.02)
L	0.03(0.03)	-	1.00	0.03(0.03)	-
			Line R		
NBA	0.90(0.18)	1.10(0.18)	8.21(0.15)	0.09(0.02)	0.11(0.02)
NW	0.59(0.14)	1.12(0.15)	7.10(0.13)	0.07(0.02)	0.13(0.02)
L	0.02(0.01)	-	1.00	0.02(0.01)	-

σ^2_a = Additive variance; σ^2_p = Permanent environmental variance; σ^2_e = Residual variance; h^2 = Heritability; p^2 = Ratio of the permanent environmental variance to the phenotypic variance; NBA = Number of kits born alive; NW = Number at weaning; L = Longevity.

4.4.2 Variance components for the percentage of days in each physiological status

Heritability estimates and their standard errors for the percentages of days in each physiological status are presented in Table 4.4. The heritability estimates were low values and ranged from 0.02±0.02 to 0.11±0.05, 0.01±0.03 to 0.06±0.03, 0.01±0.01 to 0.10±0.03, 0.03±0.02 to 0.10±0.09, 0.06±0.03 to 0.19±0.06 and 0.01±0.03 to 0.11±0.03 for U/NL, P/NL, NP/L, U/L, P/L and NP/NL, respectively. To our knowledge these are the first reports on heritability estimates for these traits.

Table 4. 4 Heritability estimates (standard error) of the percentage of days in each physiological status for the different lines.

Trait	A	V	H	LP	R
U/NL	0.06(0.02)	0.02(0.02)	0.11(0.05)	0.06(0.05)	0.05(0.02)
P/NL	0.05(0.02)	0.01(0.02)	0.01(0.03)	0.01(0.03)	0.06(0.03)
NP/L	0.10(0.03)	0.01(0.01)	0.06(0.05)	0.02(0.04)	0.02(0.02)
U/L	0.09(0.03)	0.05(0.02)	0.07(0.05)	0.10(0.09)	0.03(0.02)
P/L	0.10(0.03)	0.06(0.03)	0.14(0.07)	0.19(0.06)	0.06(0.03)
NP/NL	0.06(0.03)	0.11(0.03)	0.01(0.03)	0.01(0.04)	0.03(0.02)

U= Before palpation test; P= After positive palpation test; NP= After negative palpation test; L= Lactating; NL= Non-lactating.

4.4.3 Genetic and environmental correlations between prolificacy traits and longevity

Estimates of the genetic and environmental correlations between prolificacy traits and longevity and their standard errors for the different lines are presented in Table 4.5. Negative values of the correlations represent a favourable association between longevity and prolificacy traits. In the sense that both genetic and environmental factors increasing litter size are associated to lower hazard and consequently a higher longevity. The only line for which it can be said the genetic correlation between NBA and NW, and hazard was significantly different from zero was the LP line. However it must be also noted that the reported standard error were computed assuming that the fixed variances were correct, and consequently they underestimated the true standard errors (Tarres et al., 2006 and Sánchez et al., 2006). For the line H, the highest genetic correlations were estimated but the standard errors were also higher, thus these correlations cannot be declared as statistically different from zero. Low values of the estimated genetic correlations between longevity and prolificacy are in agreement with the results of Chapter 3, observing negligible changes of the additive variance when Model 1 was compared to Model 4 (excluding NBA).

Regarding the environmental correlations, they tend to be always favourable but also very close to zero. In spite of their low magnitude for the case of those between hazard and NW they can be considered as significantly different from zero. Our results are in accordance with those reported by Sánchez et al. (2006), who studied the same parameters in line V. They observed that the genetic correlations between the hazard and each of NBA and NW were 0.16±0.093 and -0.17±0.114, respectively. Also, they stated that the environmental correlation estimates between the hazard and NBA or NW were negative: -0.11±0.016 and -0.01±0.019, respectively. As mentioned before, the studies that assessed the effect of long-term selection for litter size traits on the length of productive life in rabbits are very scarce. To our knowledge, there are only two studies concerned with this relationship. One by Rinaldo and Bolet (1988), who compared the production of female rabbits selected during 7 generations on litter size at weaning of the first three litters to the performance of a control line. They did not found significant differences between the two lines neither for productive life-time nor for total number of litters. The other study is by Theilgaard et al. (2006), who found that the selection for litter size at weaning during 12 generations in two maternal lines had no significant effect on the longevity of their crossbred does. In an experiment of divergent selection for longevity, Larzul et al. (2014) found that the differences between the high and low lines of INRA 1077 rabbits with respect to prolificacy traits were not significant. They suggested that this result may be an indicator of low correlation between longevity and prolificacy. In pigs, Serenius and Stalder (2004) stated that the estimated genetic correlations between length of productive life and number of weaned piglets were 0.39±0.16 and 0.30±0.16 in Finnish Landrace and Finnish Large White breeds, respectively. They added that the phenotypic correlation between the two traits in both breeds was 0.12. Another study by Sobczyńska et al. (2013) reported that the number of piglets born at first litters was genetically correlated with lifetime pig production.

They found that the genetic correlation between the two traits was 0.326±0.039 in the Polish Large White sows, and was 0.200±0.036 in the Polish Landrace sows. So it can be concluded that in pigs the evidence of positive genetic association between longevity and prolificacy is stronger than in lines of rabbits.

Table 4. 5 Genetic and environmental correlations (standard error) between prolificacy traits and longevity in the different lines.

Line Traits	A	V	H	LP	R
$NBA - L^{*r_g}$	0.01(0.01)	0.01(0.01)	0.16(0.20)	0.09(0.02)	-0.12(0.33)
$NW - L^{*r_g}$	0.01(0.02)	0.01(0.01)	0.17(0.23)	0.11(0.02)	-0.44(0.53)
$NBA - L^{*r_e}$	-0.01(0.01)	-0.02(0.01)	-0.07(0.05)	-0.04(0.04)	0.01(0.03)
$NW - L^{*r_e}$	-0.05(0.02)	-0.05(0.01)	-0.12(0.05)	-0.10(0.04)	-0.05(0.03)

NBA = Number of kits born alive; *NW* = Number at weaning; L^* = Longevity; r_g = Genetic correlation; r_e = Environmental correlation.

4.4.4 Genetic and environmental correlations between percentage of days in the different physiological statuses and longevity

As shown in the previous chapter, the exclusion of the physiological status effect from the model of analysis of longevity led to an increase in the estimated additive variance by about 51, 39, 38, 83 and 75% in the lines A, V, H, LP and R, respectively. These changes in the estimated additive variance could be indicators of the existence of genetic correlation between longevity and the percentage of days an animal spend in the different physiological statuses. This means that part of the genetic differences for longevity could be related to the way in which the risk of death or culling of the female changed with the physiological status and to the genetic determination of the physiological status pattern along the life of the animals. Indeed, the association between the doe’s longevity and its physiological status could be expected as both are affected by fertility and health of the doe.

The estimates of genetic correlation seem to be important in some cases for all lines, specially the correlations with U/NL, P/NL and P/L (Table 4.6). In these cases the estimates were positive showing that the physiological statuses U/NL and P/NL are indicators of low fertility and possible health problems; and P/L correspond to does with low kindling intervals that could suffer exhaustion. However, due to the high standard errors of the estimates it has not been possible to prove that the genetic correlations were significantly different of zero. On the other hand, the estimates of environmental correlation were in general significantly different from zero for 23 of 30 estimates (Table 4.6). The environmental correlations between longevity and each of U/NL, P/NL and P/L were significant in all lines and represent unfavourable associations between them, following the same pattern commented for the genetic correlations.

Taking into account the noticeable change of the estimated additive variance of longevity in the five rabbit lines when excluding the physiological status effect from the model of analysis, the physiological status should not be included in the models of analysis of longevity.

Table 4. 6 Genetic and environmental correlations (standard error) between physiological status traits and longevity in the different lines.

Line Traits	A	V	H	LP	R
$U/NL-L^{*r_g}$	0.24(0.15)	0.18(0.40)	0.20(0.34)	0.47(0.47)	0.23(0.23)
$P/NL-L^{*r_g}$	0.16(0.16)	0.24(0.44)	0.11(0.54)	-0.70(0.50)	0.38(0.23)
$NP/L-L^{*r_g}$	-0.09(0.12)	0.03(0.47)	-0.07(0.47)	-0.08(0.48)	0.07(0.61)
$U/L-L^{*r_g}$	0.02(0.13)	-0.07(0.19)	0.14(0.54)	-0.05(0.57)	0.13(0.35)
$P/L-L^{*r_g}$	0.12(0.14)	0.12(0.13)	0.25(0.31)	-0.19(0.24)	0.21(0.38)
$NP/NL-L^{*r_g}$	-0.06(0.18)	-0.14(0.20)	-0.05(0.73)	0.07(0.88)	-0.15(0.42)
$U/NL-L^{*r_e}$	0.27(0.02)	0.36(0.02)	0.24(0.05)	0.34(0.05)	0.21(0.03)
$P/NL-L^{*r_e}$	0.25(0.02)	0.31(0.02)	0.37(0.04)	0.33(0.04)	0.38(0.03)
$NP/L-L^{*r_e}$	-0.12(0.02)	-0.15(0.02)	-0.10(0.05)	-0.22(0.05)	0.03(0.03)
$U/L-L^{*r_e}$	0.03(0.02)	-0.08(0.02)	0.01(0.05)	-0.05(0.06)	0.16(0.03)
$P/L-L^{*r_e}$	0.21(0.03)	0.14(0.02)	0.23(0.06)	0.12(0.06)	0.33(0.04)
$NP/NL-L^{*r_e}$	-0.06(0.03)	-0.04(0.03)	-0.10(0.05)	-0.09(0.06)	-0.15(0.03)

U= Before palpation test; *P*= After positive palpation test; *NP*= After negative palpation test; *L*= Lactating; *NL*= Non-lactating; L^* = Longevity; r_g = Genetic correlation; r_e = Environmental correlation.

4.5 CONCLUSIONS

Low estimates of the genetic and environmental correlations between longevity and each of number of kits born alive and number of weaned in five lines of rabbits were found. Longevity and prolificacy cannot be considered as antagonistic objectives of selection in the rabbit breeding programs. There were evidences of non-negligible genetic correlations between the doe's longevity and the percentage of days she spend in each physiological status in the five lines of rabbits, but their high standard errors precluded an accurate confirmation. These results show that longevity and physiological status are correlated, probably through the influence of fertility and health of the doe in both traits.

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Chapter 5

Functional longevity in five rabbit lines founded on different criteria: Comparison at foundation and at fixed times after selection

5.1 ABSTRACT

The objective of the present study was to compare five Spanish rabbit lines in terms of functional longevity. Four of them are maternal lines (A, V, H and LP) founded on different criteria and being selected for litter size at weaning. The fifth line is the paternal line R, founded and selected for postweaning daily gain from 28 to 63d. These lines are currently in the 44th, 39 th, 23th, 8th and 32th generations, respectively. Cox proportional hazard models under a Bayesian approach were used to perform two comparisons between the lines. The first comparison was done at the origin of the lines, involving the complete data set (from March 1980 to March 2013; records of 15,670 does), and the complete pedigree (19,405 animals), so the effect of selection was considered. The second comparison was done at fixed times through the selection process when all lines shared the same environmental and management conditions (from March 1997 to September 1998 and from March 2011 to September 2012). For the second comparison the same model as the first comparison was used, but excluding the additive effects from the model of analysis, and involving only the data corresponding to each period, so the differences between the lines were not dependent on the additive values of the animals. At their foundation, lines V, H and LP showed a substantial superiority over line A. The line R also had higher risk of death or culling with relevant differences when compared to V, H and LP lines. The line LP had the longest productive life compared to the other lines; this may be a consequence of its foundation process. The maximum relative risks were observed between the lines LP and R (0.239), and between LP and A (0.317). This means that at foundation it was 0.239 and 0.317 times more likely for a LP doe to be culled/died than for a R and A female, respectively. The interactions between year-seasons and the lines were important and affected the differences between the lines at their origin. During the two periods of the comparison at fixed time, lines A and R showed low longevity compared to the other lines. However, as the selection process evolves, the differences between them and the other lines were reduced, which demonstrate the importance of natural selection in these lines. The predicted differences between the four maternal lines match well the phenotypic differences computed at the fixed times of comparison, indicating that the genetic model is suitable to describe the longevity records in these populations, although, this was not the case for the paternal line R. It could be concluded that the average longevity of a population greatly depends on the criteria followed for the foundation of this population. Along the generations of selection for litter size, the differences of longevity between lines tend to decrease, due to the action of the natural selection in the lines of lower longevity.

Keywords: line foundation, functional longevity, maternal lines, survival analysis, rabbits.

5.2 INTRODUCTION

Selective breeding to increase the length of productive life could help to reduce costs attributed to replacements. The main difficulty in improving longevity through the traditional breeding methods is the time required to obtain relevant information (Larzul et al., 2014). The studies analysing differences in longevity among lines of farm animals especially rabbits are actually scarce. Relevant differences in direct genetic effects for functional longevity defined as the ability to delay involuntary culling were found between maternal lines of rabbits highly selected for litter size at weaning (Piles et al., 2006a). The consequences of any selection experiment of a rabbit line on a concrete trait could be limited by the foundation history and the criteria used to constitute this line. One way to quantify these consequences is to estimate the differences respect to the desired trait between some lines sharing the same environmental and management conditions at their origin and after some generations of selection. In rabbits, meat production is based on the use of crossbred does, coming from the cross of two maternal lines (Baselga, 2004). The length of productive life of the crossbred does will depend on both the longevity of the maternal lines involved in the cross and on heterotic effects that might appear. Consequently it is important to compare the longevity of lines involved in the cross and to assess how these differences evolve during the selection processes of the lines. So, the aim of this study was to compare five Spanish lines of rabbits in terms of longevity, at their foundation and at different fixed periods during their programs of selection, four of these lines are maternal lines which are being selected for litter size at weaning and founded on different criteria, and one paternal line selected for post-weaning daily gain from 28 to 63d.

5.3 MATERIALS AND METHODS

5.3.1 Animals

Data used in the present study were collected from five Spanish lines of rabbits, four of them are maternal (A, V, H, LP) and the fifth one is a paternal line (R). These lines are reared at a selection nucleus located in the farm of the Department of Animal Science, Polytechnic University of Valencia (UPV). The records were collected along the generations of selection of these lines from March 1980 to March 2013. The processes of foundation and selection and management programs of these lines were explained in Chapter 3.

Management of animals in line R is somewhat different compared to other lines, where in the last generations the does were artificially inseminated and the candidates for selection were genetically evaluated exclusively based on their phenotypic values, i.e. individual selection. Each sire contributes a son to the next generation and does are selected weekly at a rate of around 20%, referred to the average growth of the previous four weeks. Selection was in non-overlapping generations until the 25th generation. The generation interval is about 6 months and the estimated response to selection was about 0.5 g/day per generation (Estany el al. 1992), while in maternal lines the generation interval is about 9 months and the response to selection was ranged from 0.076 (Tudela et al., 2003) to 0.085 (García and Baselga, 2002) kit weaned per parturition by generation.

5.3.2 Data and Statistical Models

The analysed trait (LPL), the individual records and the total number of animals in the data and pedigree files were the same as explained before in Chapter 3. The number of does for the comparisons at foundation and at fixed times are shown in Table 5.1.

Table 5. 1 Number of does involved in the study.

Line	Foundation[1]	First period[2]	Second period[3]
A	4,986	348	320
V	5,275	350	362
H	1,156	317	-
LP	1,224	-	333
R	3,029	243	266
All lines	15,670	1,258	1,281

[1] = Total number of does; [2] = Number of does at first period comparison; [3] = Number of does at second period comparison.

For the comparison between lines at their origin, involving the complete data set from the foundation of each line until March 2013 and including the full pedigree, a complete genetic model (**CM**) was used including the systematic effects of line-year-season combination (LYS), positive palpation order (OPP), and number born alive at each kindling (NBA) as time-dependent factors; in addition to the additive value of the animal as a random effect. In details, the **CM** model was:

$$h_i\left(\mathrm{t}|\mathbf{x'}_i(\mathrm{t})\right) = h_0\ (t)\exp\{\mathbf{x'}_i(\mathrm{t})_{\mathbf{LYS}}\boldsymbol{\beta}_{\mathbf{LYS}} + \mathbf{x'}_i(\mathrm{t})_{\mathbf{OPP}}\boldsymbol{\beta}_{\mathbf{OPP}} + \mathbf{x'}_i(\mathrm{t})_{\mathbf{NBA}}\boldsymbol{\beta}_{\mathbf{NBA}} + \mathbf{z'}_i\,\mathbf{u}\}$$

where $h_i(t|\mathbf{x'}_i(t))$ is the hazard of animal i at time t, for time-dependent factors, affected by covariates indicated by $\mathbf{x}_i'(t)=\{\mathbf{x}_i'(t)_{\mathbf{LYS}}, \mathbf{x}_i'(t)_{\mathbf{OPP}}, \mathbf{x}_i'(t)_{\mathbf{NBA}}, \mathbf{z}_i'\}$; $h_0(t)$ is the baseline hazard function at time t, approximated by a step-wise function given by $h_0(t) = h_{0m}$ for $t \in [\tau_{m-1}, \tau_m]$; $m = 1, \dots, M+1$, where $\tau_1, \dots, \tau_M$ are the M different ordered survival times, $\tau_0 < \tau_1 < \cdots < \tau_M < \tau_{M+1}$; $\tau_0 = 0$ and $\tau_{M+1} = \infty$. $\boldsymbol{\beta}_{\mathbf{LYS}}$, is the vector of regression coefficients for the line-year-season (**LYS**) combinations with 212 levels, where the year-season was defined by 6 months' time intervals. The number of levels was 63, 63, 17, 20 and 49 for the subsets of A, V, H, LP and R lines, respectively. $\boldsymbol{\beta}_{\mathbf{OPP}}$, is the vector including the effect of the three levels of the positive palpation order (**OPP**) (1, 2 and 3 or more positive palpation orders), the changes of level in this factor occurred after every pregnancy test. $\boldsymbol{\beta}_{\mathbf{NBA}}$, is the vector including the effects of 5 classes of number born alive in each kindling (**NBA**); the first level corresponded to does that had 0 NBA, the second level to does that had 1 to 4 born alive, the third to 5 to 8 born alive, and so on until the fifth level which corresponded to does that had at least 12 born alive. The changes of levels in this time-dependent factor occurred at parturition. Because only females with at least one litter were considered in the analysis, there were no nulliparous does. Finally, u_i is the additive genetic effect of the animal i, this factor was assumed to follow a priori a multivariate normal distribution with mean 0 and (co)variance $\mathbf{A}\sigma^2_a$, where **A** is the numerator relationship matrix and σ^2_a is the additive genetic variance. Prior distributions for the parameters were defined in the same way as in Sánchez et al. (2006); λ_i were assumed to be i.i.d., $\lambda_i = \frac{1}{\lambda_i}$, the elements of $\boldsymbol{\beta}$ were assumed to be i.i.d. following a bounded uniform distribution. The estimation of model parameters was conducted by a Bayesian approach, obtaining estimates from the marginal posterior distributions using a Gibbs sampling algorithm. The Gibbs sampling was implemented in a Fortran 90 program, in which the subroutines by Gilks and Wild (1992) for adaptive rejection sampling (ARS) were used (Sánchez et al., 2006) and the program is available upon request from the authors. The Gibbs sampler algorithm comprised 200,000 iterations, discarding the first 20,000 in order to allow for the algorithm to reach convergence to the marginal posterior distributions. Afterwards, one sample in each 20 was saved to avoid high correlations between consecutive samples. The post-Gibbs analysis used to calculate the parameters of interest of the marginal posterior distributions was implemented with the coda package of the R program. Convergence of the chains of the parameters and contrasts of interest was assessed by using the Z-criterion of Geweke (Geweke, 1992).

Considering the genetic heterogeneity between the five lines, and using the estimated additive variance for each line, the fixed and additive effects of the model were estimated, including LYS effects. Because the additive effects were considered, taking into account the response to selection, the estimates of the difference between lines refer to the line effects at foundation time. Thus, the contrast of the differences between each pair of lines at foundation is computed as the difference of the averages, for each line, of the line-year-season effects corresponding to the year-seasons common to both lines. The periods in which each pair of lines were sharing the same environmental and management conditions were from March 1983 to September 2003 and from March 2006 to March 2013 for lines A and V, from March 1997 to September 1998 for lines A and H, from March 2006 to March 2013 for lines A and LP, from March 1990 to March 2013 for lines A and R, from March 1997 to September 1998 for lines V and H, from September 2004 to March 2013 for lines V and LP, from March 1990 to September 2003 and from March 2006 to March 2013 for lines V and R; from March 1997 to September 1998 for lines H and R; and from March 2006 to September 2013 for lines LP and R. The lines H and LP only had one year-season in common for this reason the contrast between them was not conducted out.

It is possible to compute real differences between lines at different periods of time shared by some of them, without relying on the genetic model and by only using the records of the defined periods of the lines to be compared. Thus, the model of analysis should be the one previously defined, removing the additive genetic effect (incomplete model; **IM**). In this case the line effects refer to the real genetic merit of these lines at the time of comparison. The difference between two lines at a defined period was computed as the difference between the averages for each line of the line-year-season effects of the period. The periods chosen for comparison were arbitrarily defined by the last three year-seasons shared by four of the lines under the same management conditions. Consequently the comparison between lines A, V, H and R was from March 1997 to September 1998 and from March 2011 to September 2012 to compare the lines A, V, LP and R. It is also possible to predict the differences between the lines at the defined periods using the results of the analysis with the **CM** model and complete data set. The predicted difference between two lines will be computed in the same way as the comparison at foundation but limited to the year-seasons corresponding to the period covering the last three year-seasons shared by four of the lines, adding the difference between the averages of the additive values of the animals of each line performing during that period. Then, the estimated differences resulted from **IM** model can be compared with the predicted ones resulted from **CM** model as a way to check the adequacy of the **CM** model to explain the complete longevity data set.

5.4 RESULTS AND DISCUSSION

5.4.1 Comparison between lines at foundation

Monte Carlo standard errors were very small in all cases and they are not showed in the tables. Geweke test did not detect lack of convergence in any case.

The comparison among lines at their foundation is shown in Table 5.2. The contrasts are estimable functions between each pairs of lines through the years-season in which both lines were subjected to the same environmental and managerial conditions. Using all data and the full pedigree, the additive effects of the animals were considered in the model, the selection response was accounted for by this effect, and consequently, the effects of the lines (included in the line-year-season combination) expressed the values at their foundation. The lines H and LP had only one year-season in common and for this reason the comparison between them has not been carried out. The lines V, H and LP showed a substantial superiority over line A. The line R had higher risk of death or culling with relevant differences when compared to V, H and LP lines. The maximum relative risks were observed between the lines LP and R, and between LP and A. The relative risk describes how much more likely it is that culling or death occurs within one level of a given factor relative to another level of the same factor. For instance, at foundation it was 3.125 times more likely for a Line A doe to be culled/died than for a LP doe (Table 5.2). Line LP was created from does that had at least 25 parities (Sánchez et al., 2008). The results showed in Table 5.2 have apparent inconsistencies, for example, the difference between lines A and V at their foundation was 0.495 and between lines A and LP was 1.148. Their difference, (1.148-0.495) is not exactly 0.436, the contrast between lines V and LP. This deviation between the two values is due to the different sets of year-seasons involved in each particular contrast and to the inclusion of the line-year-season interaction in the model.

The longer productive life of LP does could be considered as an indicator of the successful foundation procedure of this line. On the other hand, the line A was created by mating does and bucks of the New Zealand White breed belonged to commercial populations maintaining the standard morphological characteristics of the breed. In addition, line A had a high susceptibility to enterocolitis disease which was present during some periods shared with the other lines (Ragab and Baselga, 2011). Piles et al. (2006a) found relevant differences in the genetic effects for functional longevity between maternal rabbit lines A, V and Prat and the crossbred females from them. They stated that a A doe was twice as likely to be replaced than a crossbred Prat × A doe, and in general the genetic types with the highest relative risks were those in which the A line participated. In another study comparing two maternal lines of rabbits, Sánchez et al. (2008) indicated the superiority of the line LP over the line V in survival ability, especially at later cycles. They attributed this result to the selection procedure in the LP line which was focused on late survival. Moreover, the comparison between LP and V lines was not a comparison at foundation time because for V line only the closest relationships were considered in the study. In contrast, in the present study all the available pedigree information was used. Line R showed higher risk at foundation compared to the other lines, and the differences between line R and both LP and V lines were relevant; this may be due to its foundation procedure where the foundation criteria was more focused on the standard morphological characteristics of the founder animals. Considering that line R was created by mating animals from Californian breed with animals from another synthetic line created by mating animals of three commercial paternal lines (Estany et al., 1992).

Table 5. 2 Differences between the lines at foundation for longevity (log-hazard) estimated with the complete genetic model and all data.

Contrast	PM[1]	PSD[2]	RR[3]	$HPD_{95\%}$[4]	P(%)[5]
A-V	0.495	0.230	1.640	0.029 , 0.936	99
A-H	0.699	0.280	2.012	0.162 , 1.270	99
A-LP	1.148	0.321	3.152	0.510 , 1.753	100
A-R	-0.125	0.240	0.882	-0.611 , 0.345	77
V-H	0.050	0.192	1.051	-0.333 , 0.418	60
V-LP	0.436	0.192	1.547	0.072 , 0.819	99
V-R	-0.620	0.158	0.538	-0.935 , -0.321	100
H-R	-0.344	0.185	0.709	-0.734 , -0.003	97
LP-R	-1.432	0.156	0.239	-1.725 , -1.119	100

[1] = Marginal posterior mean; [2] = Marginal posterior standard deviation; [3] = Relative risk = exp(contrast); [4] = Marginal posterior highest density region covering 95% of the density; [5] = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

5.4.2 Comparison between lines at fixed periods

The estimated differences between the lines A, V, H and R from March 1997 to September 1998 and between the lines A, V, LP and R form March 2011 to September 2012 are presented in Table 5.3. The last period reflects the current situation of the four lines. Lines A and R had a greater risk of death or culling than lines V and H, which was the same trend as in the comparison at the foundation time of these lines. The contrasts show the inferiority of the line A for longevity over the other maternal lines during the two periods of comparison. This result is in agreement with those of Ragab et al. (2011) who found that line A was more sensitive to the risk factors compared to the V and LP lines. The LP does had a lower risk of death or culling compared to A, V and R lines, this result could be explained, again, as a direct consequence of the foundation process of the LP line. The same result was found by Sánchez et al. (2008) who reported that the LP line had a longer reproductive life than the V line. In general, as the selection process evolves, the differences between the lines changed and were reduced. This may be attributed to the different sets of year-seasons considered in the different moments of comparisons, in addition to the important role of the natural selection that had higher intensities in the lines of lower longevity, in the sense that in animals with lower longevity, the probability of dying before leaving progeny selected for litter size is higher than in animals having higher longevity. Moreover, the selected progeny of parents with low longevity would have a higher probability of dying before reaching the maturity. This phenomenon can be clearly observed in line A which had low longevity at its foundation and has greatly improved its longevity along many selection generations since the foundation until the two periods of comparison at fixed times. This can be seen in Table 5.4, as the differences in the breeding values of animals of each line involved in the comparison were favoured the line A compared to the other lines. This progress of the line A is consistent with the genetic trend drawn by its relatively higher heritability (0.17) estimated in Chapter 3. The line R also had low longevity at its foundation and has improved its longevity throughout less number of selection generations and lower heritability than line A (Chapter 3). The correlated response resulted from the selection for litter size at weaning in the four maternal lines is not expected to be responsible for the reduction of the differences between the lines along the generations of selection, since the genetic correlations between longevity and prolificacy were irrelevant (Chapter 4). However, the genetic correlation between longevity and the selection criteria in line R has not been studied.

The differences between lines at fixed times using the data limited to these times but using the **CM** model are presented in Table 5.4. Comparing these differences and the corresponding differences estimated using the **IM** model; show that they are relatively similar in the case of the four maternal lines (A, V, H and LP). This means that the genetic model used for the prediction of breeding values and the estimation of the differences between the lines at origin was suitable to describe this longevity data. A similar result was obtained by Ragab and Baselga (2011), when comparing reproductive traits and by Mínguez et al. (2015), when comparing growth traits in the same four lines. For the paternal line R, the differences estimated using **CM** model did not match well those estimated using the **IM** model. The consequence is that for line R, which has characteristics very different to the maternal lines; the model used is less adequate than in those lines.

Table 5. 3 Differences between the lines for longevity (log-hazard) at fixed times estimated with the incomplete model and data of the fixed times.

Contrast	**PM[1]**	**PSD[2]**	**RR[3]**	**$HPD_{95\%}$[4]**	**P(%)[5]**
			March 1997 - September 1998 (First period)		
A-V	0.395	0.111	1.484	0.177 , 0.611	99
A-H	0.295	0.119	1.343	0.052 , 0.515	99
V-H	-0.099	0.121	0.906	-0.347 , 0.129	79
A-R	0.148	0.115	1.160	-0.078 , 0.374	90
V-R	-0.247	0.121	0.781	-0.488 , -0.012	98
H-R	-0.147	0.128	0.863	-0.400 , 0.102	88
			March 2011 - September 2012 (Second period)		
A-V	0.122	0.120	1.130	-0.121 , 0.365	83
A-LP	0.564	0.156	1.758	0.270 , 0.881	99
V-LP	0.442	0.150	1.556	0.145 , 0.735	99
A-R	0.015	0.134	1.015	-0.248 , 0.271	54
V-R	-0.107	0.132	0.899	-0.364 , 0.149	79
LP-R	-0.550	0.163	0.577	-0.852 , -0.227	100

[1] = Marginal posterior mean; [2] = Marginal posterior standard deviation; [3] = Relative risk = exp(contrast); [4] = Marginal posterior highest density region covering 95% of the density; [5] = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

Table 5. 4 Differences between the lines for longevity (log-hazard) at fixed times estimated with the complete genetic model and data of the fixed times.

Contrast	**PM**[1]	**D**[2]	**PSD**[3]	**RR**[4]	**HPD$_{95\%}$**[5]	**P(%)**[6]
			March 1997 - September 1998 (First period)			
A-V	0.314	0.648 , -0.334	0.113	1.369	0.087 , 0.532	99
A-H	0.251	0.699 , -0.448	0.120	1.285	0.008 , 0.479	98
V-H	-0.063	0.050 , -0.113	0.125	0.939	-0.302 , 0.181	69
A-R	-0.073	0.355 , -0.428	0.111	0.930	-0.285 , 0.143	74
V-R	-0.387	-0.293 , -0.094	0.114	0.679	-0.622 , -0.179	100
H-R	-0.324	-0.344 , 0.020	0.122	0.723	-0.570 , -0.089	100
			March 2011 - September 2012 (Second period)			
A-V	0.104	0.655 , -0.551	0.127	1.110	-0.152 , 0.345	80
A-LP	0.710	1.332 , -0.623	0.157	2.034	0.412 , 1.029	100
V-LP	0.605	0.677 , -0.072	0.153	1.831	0.298 , 0.896	100
A-R	-0.592	-0.251 , -0.342	0.127	0.553	-0.835 , -0.341	100
V-R	-0.697	-0.906 , 0.209	0.121	0.498	-0.930 , -0.456	100
LP-R	-1.302	-1.583 , 0.281	0.154	0.272	-1.614 , -1.010	100

[1] = Marginal posterior mean; [2] = Part of PM due to differences at foundation, and to differences in the additive values of the animals of each line involved in the comparison; [3] = Marginal posterior standard deviation; [4] = Relative risk = exp(contrast); [5] = Marginal posterior highest density region covering 95% of the density; [6] = Probability of the difference being >0 when the contrast >0 and probability of the difference being <0 when the contrast <0.

5.5 CONCLUSIONS

Relevant differences were detected between the lines at their origin, which could be explained by the foundation criteria. These differences were also affected by the interactions between the year-seasons and lines. The average longevity of a population greatly depends on the criteria followed for the foundation of this population. It seems that the breed criterion is less suitable than other criteria more closely related to production, mainly the criteria based on hyperlongevity. Along the generations of selection for litter size, the differences of longevity between lines tend to decrease, due to the action of the natural selection in the lines of lower longevity. The predicted differences between the four maternal lines match well the phenotypic differences between them, indicating that the genetic model is suitable to describe the longevity records in these populations. This was not the case for the paternal line R.

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Chapter 6

GENERAL DISCUSSION

The relatively economic importance of longevity in rabbit production comes from its relation with the replacement rate, welfare, ethics and social concerns. The replacement rate in rabbits for meat production is high and ranged from 114 to 120 % yearly (Rafel et al., 2001 and Prieto et al., 2014) with about 50% of the dead or culled does replaced during their first 3 parities (Rosell, 2003).

Till now the consideration of longevity, as a breeding objective, only has been done in one work, as a foundation criterion of the Spanish long-lived-productive (LP) line (Sánchez et al., 2008), and as a selection criterion in a divergent selection experiment of the INRA1077 rabbit line (Larzul et al., 2014). The problem that arises in improving longevity through conventional breeding methods is mainly attributed to the time required to obtain a reasonable database which implies large generation intervals. Although, it has been demonstrated experimentally that reproductive life and number of parities can be improved by selection on phenotypic performance in mice (Farid et al., 2002), and it has been shown that the selection for functional longevity using survival analysis can modify lifetime reproductive traits in rabbits (Larzul et al., 2014). However, in the last experiment of divergent selection, the symmetry of the response was not assessed.

In Spain, long-term selection experiments were started since the year 1976 aiming to create new lines or rabbits for meat production in the selection nucleus belonged to the Department of Animal Science, Universidad Politécnica de Valencia (UPV). The maternal rabbit lines resulted from these experiments are the A, V, H and LP lines. All these lines differ in their foundation histories, but being selected for litter size at weaning accounting for the milk production and maternal ability. The only paternal line raised in this nucleus is the line R, where its selection criterion is the average daily gain from weaning till slaughtering at 63 days. In addition, the lines differ in the length of their selection programs. So, the UPV’s lines could be considered as useful genetic materials to study the genetic determination of longevity by estimating its heritability, checking the genetic influences of time-dependent factors such as the parity orders, the physiological state and the number of kits born alive on the genetics of longevity, examine the genetic and environmental association between prolificacy traits and longevity, and to quantify the consequences of the different foundation criteria on longevity throughout the selection processes of these lines.

The genetic heterogeneity between and within rabbit lines is important because it is a factor which determine the expected improvement in the desired trait. In rabbits, the studies concerning genetic variability for longevity are scarce. These studies have considered a very small number of rabbit lines (Piles et al., 2006 and Sánchez et al., 2004) and have showed the dependency of the estimates on the model of analysis (Garreau et al., 2001). In the present thesis, the genetic heterogeneity between the five rabbit lines was analysed through the estimation of the additive variance for each line separately and for all lines jointly (Chapter 3). Four different Cox proportional hazard models under a Bayesian approach were used. The first model (Model 1) included, as time-dependent factors, the positive palpation order (OPP), the physiological status (PS), and the number of born alive (NBA), and the other three models were the same as the first one but excluding OPP (Model 2), or PS (Model 3), or NBA (Model 4) to quantify the changes in the additive variance induced by the exclusion of each one of the factors. The estimated heritabilities were low and within the range of the previous estimates. Line H had the highest heritability estimate (0.14) but with a very wide $HPD_{95\%}$ (0.003, 0.292). This low precision is consequence of the low number of records in this line. The paternal line in this study, line R, had the lowest estimate (0.02). The precision was greater in the case of lines A and V due to the larger number of records; in these cases around 40 generations of data were covered. In spite of the large variation of the heritability estimates, the corresponding $HPD_{95\%}$ always overlapped and consequently the hypothesis of all lines having the same heritability cannot be discarded. Comparing the results of the different models, it can be shown that correcting for physiological status of the female (Model 3) removed around 51, 39, 38, 83 and 75% of the additive variance in lines A, V, H, LP and R, respectively. Hence, genetic differences for functional longevity should be related to the way in which the risk of the females changed with the physiological status and the life term physiological status pattern has genetic determination and it is expected to be genetically correlated with longevity. These findings are in agreement with those reported by Piles et al. (2006). A genetic correlation between longevity and life-term physiological status pattern could be expected if it is taken into account that both are affected by the fertility and health of the does. This hypothesis was specifically assessed in Chapter 4. In the LP line, the change in the additive variance using Model 3 was very high (83 %), this could be related to the highest values in this line for the contrasts between different levels of the physiological status which in turn could be a consequence of the foundation criterion of this line that increased the longevity and could produce a range effect on all the factors affecting the trait. However, excluding OPP or NBA nearly did not change relevantly the additive variance estimate of the longevity. Regarding the genetic trend for longevity, it can be observed that the highest slopes were observed for lines H and A. The differences in genetic trend between lines can be partly explained by the differences of the heritability and the differences in intensity of natural or unintended selection for longevity in the different lines. The intensity of natural selection in a line is clearly related to its longevity, animals with lower longevity have higher probability of dying before leaving progeny to be selected as reproducing animals for the next generation. In relation to the effect of OPP on longevity, the highest differences of hazard were observed between OPP1 and OPP3, followed by the contrasts between OPP2 and OPP3. The maximum difference of hazard between the first and third level of OPP was in the LP line (1.30±0.34). The selection conducted when founding this line, extremely long-lived animals, would promote survival ability at later ages rather than at early ages (Sánchez et al., 2008). The hazard of death or culling was greater for the first two parities. In the first and second parity the does are still growing and the kindling would be an important risk factor (Sánchez et al., 2004). With regard to PS effect, the results showed that non-pregnant-non-lactating females had higher risk of death or being culled than females in any other level in each one of the five lines, non-pregnant-non-lactating females are low fertility does and this is an indication of health's problems. In addition, it seems that the lactation status of the doe at mating had relatively higher importance than reproductive status in defining the hazard of animal for dying or being culled. The same pattern was observed by Sánchez et al. (2004) and Piles et al. (2006). Regarding the effect of NBA, the level including zero born alive in all the lines had associated the highest risk compared to the other levels. In addition, in line V the level including from 1 to 4 born alive had also higher risk than the levels including 5 to 8 and 9 to 12 born alive. In line H, the probabilities of the contrasts being higher (positive contrasts) or lower (negative contrasts) than zero were between 52 and 91%. These results indicate that either these contrasts have a low magnitude or that the uncertain about them is high. In the current study no voluntary culling for productive reasons was practiced in the farm. Thus, the greater risk of culling related to low litter sizes could be associated with underlying pathological disorders. Longevity was not unfavourably affected by large number born alive, and in some lines the risk of culling or death decreased with increasing the number born alive. The same pattern was previously observed by Garreau et al. (2001), Sánchez et al. (2004), Sánchez et al. (2006b) and Lenoir et al. (2013).

The estimation of the genetic and environmental association between linear and nonlinear traits is not immediate. Ducrocq et al. (2001) proposed a two-step approach for multiple trait evaluation of longevity and production traits. The main approximation relies on the replacement of raw data by pre-adjusted records, free of environmental effects and summarising repeated records of the same animal into a single value. In the current study, this approach was used to estimate the genetic and environmental correlations between longevity and prolificacy [number of kits born alive (NBA) and number of kits alive at weaning (NW)] in the five rabbit lines (Chapter 4). In this work, the estimation of genetic parameter such as heritability and the ratios of permanent environmental variance to the phenotypic variance for NBA and NW traits were marginal but necessary. The heritability estimates ranged from 0.05±0.02 to 0.11±0.01 for NBA and from 0.04±0.02 to 0.12±0.01 for NW. These estimates were in general low and tended to decrease from birth to weaning. The same pattern was obtained by García and Baselga (2002). The lowest estimates were observed in line H, line founded following a criterion of hyperprolificacy (Cifre et al., 1998).

The only line for which it can be said the genetic correlation between NBA and NW, and hazard was significantly different from zero was the LP line. Although, it should be considered that the reported standard errors were computed assuming that the fixed variances were correct, and consequently underestimated the true standard errors (Tarres et al., 2006 and Sánchez et al., 2006a). For the H line the highest genetic correlations were estimated but the standard errors were also high, thus these correlations cannot be declared as statistically different from zero. In general the genetic correlation estimates were low and this result was in agreement with the result obtained in Chapter 3, where excluding NBA effect from the model of analysis (Model 4), nearly did not change the estimate of the additive variance of longevity. Regarding the environmental correlations, they tend to be always favourable but also very close to zero. In spite of their low magnitude, the environmental correlations between hazard and NW can be considered as significantly different from zero. Sánchez et al. (2006a) obtained a similar pattern of correlations between longevity and prolificacy in line V. From these results, it can be concluded that longevity and prolificacy cannot be considered as antagonistic objectives of selection in the rabbit breeding programs.

The genetic and environmental correlation between longevity and the percentage of days that a female spend in the different physiological status during its entire life were studied, trying to explain the changes in the additive variance when removing PS from the model for the analysis of the longevity (Model 3 in Chapter 3). The pseudo-records of the proportion of days in each physiological status were adjusted for the effect of year-season in which the doe started its productive life. For the joint analysis with longevity, the pseudo-records for longevity were computed using a model in which the physiological status effect was not considered (Model 3 in Chapter 3). The heritability estimates were low values and ranged from 0.02±0.02 to 0.11±0.05, 0.01±0.03 to 0.06±0.03, 0.01±0.01 to 0.10±0.03, 0.03±0.02 to 0.10±0.09, 0.06±0.03 to 0.19±0.06 and 0.01±0.03 to 0.11±0.03 for U/NL, P/NL, NP/L, U/L, P/L and NP/NL, respectively. The estimates of genetic correlation seem to be important in some cases for all lines, specially the correlations with U/NL, P/NL and P/L (Table 4.6). In these cases the estimates were positive; this indicates an antagonist relationship between staying a large proportion of their life in these physiological statues and longevity. The physiological statuses U/NL and P/NL are indicators of low fertility and possible health problems; and P/L correspond to does with low kindling intervals that could suffer exhaustion. However, due to the high standard errors of the estimates it has not been possible to prove that the genetic correlations were significantly different of zero. On the other hand, the estimates of environmental correlation were in general significantly different from zero for 23 of 30 estimates (Table 4.6). The environmental correlations between longevity and each of U/NL, P/NL and P/L were significant in all lines and represent unfavourable associations between them, following the same pattern commented for the genetic correlations. The effects of U/NL, P/NL and P/NL estimated in Chapter 3 match pretty well these antagonist relationships, in fact the order of the effects of the different levels is the same as the magnitude of the correlations: U/NL > P/NL > P/L. However it has to be noted that these are not the levels with the strongest effect on hazard, for example NP/NL and NP/L had larger effects.

Taking into account the noticeable change of the additive variance of longevity in the five rabbit lines when excluding the physiological status effect from the model of analysis, the physiological status should not be included in the models of analysis of longevity.

The consequences of any selection experiment of a rabbit line on a concrete trait could be limited by the foundation history and the criteria used to constitute this line. One way to quantify these consequences is to estimate the differences on the desired trait between some lines selected for one trait but founded on different criteria at their origin and after some generations of selection. This was one of the major objectives of the present thesis (Chapter 5), since the four maternal rabbit lines are selected for litter size at weaning but founded according different criteria. However, the paternal line R was founded and selected for average daily gain from weaning till 63 days but its importance comes from its large use in the three-way crossing scheme as a terminal sire in commercial rabbit farms. An animal frailty model (CM) was used to estimate the differences between the five lines at their origin including the effects of the line-year-season combination (LYS), the positive palpation order (OPP) and the number born alive (NBA) as fixed factors and the additive genetic effects of the animals as a random factor. Because the additive effect was included in the model, the full pedigree was involved and all the data from the origin were included, the estimates of the difference between lines refer to the line effects at foundation; i.e. the response to selection has been accounted through the trend in the additive genetic effects. In addition, lines were compared after some generations of selection, two periods were chosen, the first period was from March 1997 to September 1998 and the second period was from March 2011 to September 2012. For this comparisons the same model as the comparison at the origin was used, but in this case the additive effect was excluded from the model (IM model), and also for this comparison only the data corresponding to each period were retained. From the solutions of the CM model and the full data set it was also possible to predict the differences between the lines at the defined periods. At their foundation, the lines V, H and LP showed a substantial superiority over line A. The line R had higher risk of death or culling with relevant differences when compared to V, H and LP lines. The line LP had the longest productive life compared to the other lines; probably a consequence of its foundation process. The maximum relative risks were observed between the lines LP and R (0.239), and between LP and A (0.317). This means that it was 3.125 times more likely for a line A doe to be culled/died at foundation than for a LP doe. The interactions between year-seasons and the lines were important and affected the differences between the lines at their origin. During the two periods of the comparison at fixed time, lines A and R showed low longevity compared to the other lines. However, as the selection process evolves, the differences between them and the other lines were reduced, which demonstrate the importance of natural selection in these lines. This phenomenon can be clearly observed in line A which had low longevity at its foundation and has greatly improved its longevity along many selection generations since the foundation until the two periods of comparison at fixed times. The differences in the breeding values of animals of each line involved in the comparison were favoured the line A compared to the other lines. This progress of the line A is consistent with the genetic trend and its relatively higher heritability (0.17) showed in Chapter 3. The line R also had low longevity at its foundation and has improved its longevity throughout less number of selection generations and lower heritability than line A (Chapter 3). The correlated response resulted from the selection for litter size at weaning in the four maternal lines is not expected to be responsible for the reduction of the differences between the lines along the generations of selection, since the genetic correlations between longevity and prolificacy were irrelevant (Chapter 4). However, the genetic correlation between longevity and the selection criteria in line R has not been studied. For the four maternal lines, the predicted differences estimated using the CM model match pretty well the differences estimated using the IM model which is an indication that the complete genetic model was suitable to analyse the data set of these rabbit populations. This was not the case for the paternal line R, line with the lowest censoring rate, and reproductive performance level very different to the maternal lines.

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Chapter 7

FINAL CONCLUSIONS

1. Low heritability estimates for functional longevity in the five rabbit lines (A, V, H, LP and R) were found, and it is not recommended to include this trait as selection criteria in rabbit breeding programs.

2. Large differences in the genetic determination of longevity might exist, but the estimation errors do not allow discarding the hypothesis of all the studied populations to have the same heritability.

3. Removing the doe's physiological status effect from the model of analysis led to an increase of the additive variance of longevity more notably for the line LP, this could be related to its foundation criteria. These noticeable increases in the additive variance recommends not include the physiological status effect in the models of analysis of longevity.

4. The risk of death or culling of the doe was higher during the first two parities, and therefore the hazard tended to decrease as the order of parity advances.

5. The risk for the non-pregnant-non-lactating level of physiological status was higher than the other levels; this is an indication of pathological and low fertility troubles.

6. The risk decreases as the number of kits born alive increases; however, it has to be considered that the does that had zero born alive had the highest risk.

7. Longevity and prolificacy cannot be considered as antagonistic objective of selection in the rabbit breeding programs, given that the genetic and environmental correlation estimates between longevity and the number of kits born alive or the number of kit at weaning were negligible.

8. Evidences of non-negligible genetic correlations between the doe's longevity and the percentage of days she spent in each physiological status were observed, but their high standard errors precluded an accurate confirmation. Although, the results show that longevity and physiological status are correlated, probably through the influence of fertility and health of the doe in both traits.

9. Relevant differences were detected between the lines at their origin, which could be explained by the foundation criteria.

10. The criterion used for founding A line seems to be the less suitable with regard to the longevity. This line was founded from animals that fulfilled the New Zealand White breed morphological standard. Other criteria more closely related to production, particularly the criteria based on hyperlongevity, used for founding the LP line seems to be more suitable to have a base population with an increased average for length of productive life.

11. The differences of longevity between lines tend to decrease as the generations of selection progresses; this result reflects the higher importance of natural selection for longevity during the selection processes of maternal and paternal lines.

12. Strong agreement has been observed between predicted and actual phenotypic differences between the four maternal lines at defined time periods. This result is an indication of the suitability of the considered genetic model. Although, this was not the case for the paternal line R, which had the lowest censoring rate, and reproductive performance level very different to the maternal lines.